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Liver and Intestinal Transplantation

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While the authors, editors, sponsor and publisher believe that drug selection and dosage
and the specifications and usage of equipment and devices, as set forth in this book, are in
accord with current recommendations and practice at the time of publication, they make
no warranty, expressed or implied, with respect to material described in this book. In
view of the ongoing research, equipment development, changes in governmental regula-
tions and the rapid accumulation of information relating to the biomedical sciences, the
reader is urged to carefully review and evaluate the information provided herein.
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Preface

Organ transplantation is increasingly complex and at the same time increasingly effective. The lengthening waiting list for cadaver organs now exceeds the supply several-fold. Despite its high profile, not more than 5,200 livers and intestines are transplanted each year in the United States with a waiting list of 18,000 patients. Most practicing physicians encounter only a few transplant recipients during a year of practice. This manual was written as a quick, but comprehensive, reference for practicing physicians and transplant professionals who interface intermittently with recipients and transplant teams. It contains ten chapters presenting the standard of practice and also controversial issues such as the ethical dilemma of long waiting lists, the living organ donor, organ banks and the national transplant network’s criteria for allocating organs to potential recipients.

We thank colleagues who have so generously shared their wisdom and insights in this volume and we solicit comments from the reader about improving content and presentation of the material.

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ACKNOWLEDGEMENT

The editors recognize and would like to thank Carolyn E. Johnson and Sue Benning for their essential skill and advice in executing the second edition of Organ Transplantation.
Northwestern Division of Organ Transplantation

Pictured (left to right): Frank Stuart, M.D., Taliia Baker, M.D., Jonathan Fryer, M.D., Joseph Leventhal, M.D., Ph.D., Alan Koffron, M.D., Dixon Kaufman, M.D., Ph.D., Michael Abecassis, M.D., M.B.A. (Chief, Division of Organ Transplantation)
Organ Allocation in the United States

THE NATIONAL ORGAN TRANSPLANT ACT (NOTA)

In 1984, the National Organ Transplant Act was passed by Congress to address the need for better coordination and distribution of scarce organs. The Act established a national task force to study transplantation issues and to create a National Organ Procurement and Transplantation Network (OPTN). The OPTN was started in 1986 and a Scientific Registry of Transplant Recipients (SRTR), a data gathering and tracking service on transplants, began operation in late 1987. Both were funded by the Health Resources and Services Administration (HRSA), an agency of the U.S. Department of Health and Human Services (DHHS), through contracts awarded to the United Network for Organ Sharing (UNOS) in Richmond, Virginia. UNOS now serves as the umbrella organization for national organ procurement, transplantation, and statistical information. The primary function of the OPTN is to maintain a national computerized list of patients waiting for organ transplants. All hospital transplant centers, organ procurement organizations, and tissue typing laboratories are required to meet the requirements for voting membership in the OPTN. Its purpose is to ensure equitable access to organs for critically ill and medically qualified patients and to guarantee that scarce organs are procured and used safely and efficiently.

ORGAN PROCUREMENT ORGANIZATIONS (OPOS)

Organ Procurement Organizations (OPOs) coordinate activities relating to organ procurement in a designated service area. There are 63 OPOs (often referred to as organ banks) throughout the United States. Their service areas do not overlap. Some include parts of a state, and others include one or more states. The Health Care Finance Administration (HCFA) of the department of Health and Human Care Finance Administration (HCFA) of the Department of Health and Human Services designates and regulates OPOs and sets the criteria by which their performance is judged. OPOs evaluate potential donors, discuss donation with family members, and arrange for the surgical removal of donated organs. OPOs are also responsible for preserving organs and arranging for their distribution according to national organ sharing policies established by the OPTN.

THE DIVISION OF TRANSPLANTATION (DOT)

Within HRSA, the Division of Transplantation (DOT), in the Office of Special Programs, administers the OPTN and the SRTR. Other DOT activities include providing technical assistance to the 63 OPOs, working with public and private organizations to promote donation, serving as a national resource to professional
associations, health providers, health insurers, state health departments, and the media about donation and transplantation, and managing the contract with the National Marrow Donor Program to administer the National Bone Marrow Registry for Unrelated Donors.

UNOS History

In the mid-1960s, an important development occurred that had a major effect on organ transplantation. It was determined that by transplanting a cadaveric donor kidney into a recipient that matched genetically, graft survival could be increased. As a result of this development, several transplant centers began to share kidneys as a means of extending kidney survival. Preliminary results of shipping kidneys between centers were successful. With this experience, the Kidney Disease and Control (KDC) Agency of the Public Health Service awarded seven contracts to transplant centers throughout the United States. The purpose of the contracts was to prove the feasibility of procuring kidneys in one place and preserving, matching, and transporting them in a viable condition for transplantation.

The Southeastern Regional Organ Procurement Program (SEROPP) was awarded one of these contracts on June 27, 1969. SEROPP originally had a membership of eight transplant programs in four states and the District of Columbia. It implemented a computerized on-line kidney matching system in December 1969.

In 1975, responding to the increase in activity, the South-Eastern Organ Procurement Foundation (SEOPF) was incorporated with 18 members in a six-state area.

Responding to requests from non-SEOPF transplant centers to utilize the computer system for registering potential recipients and sharing kidneys, the United Network for Organ Sharing (UNOS) was established in January 1977. UNOS was designed to utilize the benefits of a computerized system for matching kidneys nationally. The ultimate objective was to better utilize procured kidneys while improving outcome. UNOS granted access to the computer registry and matching program to any transplant program within the United States. The registry in the late 1970s included not only kidney recipients, but those awaiting other organs as well.

By 1982, UNOS was becoming more of a national sharing network, and because of the complexity of sharing kidneys over a large portion of the country, SEOPF and UNOS created “The Kidney Center.” The Kidney Center was staffed 24 hours a day with personnel who could run the computer and locate recipients for kidneys and other organs, arrange kidney transportation, maintain and update registry files for those who requested it, and attempt to locate organs through the UNOS/STAT system for patients who were critically ill. Recipients listed on the computer were assigned "status" codes to reflect urgency of need. When a match was found, the kidney was offered to the recipient center and transplanted there with arrangements made by SEOPF. The transportation of other organs (hearts, livers) remained the responsibility of the donor center since the recipient center sent its own team of surgeons to retrieve the non-renal organ. In 1984, the Kidney Center became known as the “Organ Center” to reflect its activity with other organs.
In anticipation of changes occurring both in the field of transplantation and in the legislative arena, UNOS was incorporated as a private, non-profit voluntary membership organization in 1984. This action was recommended by two committees, working separately, to determine if UNOS should incorporate to meet the changing demands of the transplant field. UNOS was classified for federal tax purposes as a medical, scientific, and educational organization. The primary mission of the organization was to operate the computerized national recipient registry for patients in need of transplantation and to coordinate the placement of organs procured in the United States through the Organ Center. UNOS was the only organization of its kind offering services to the entire nation. Transplant programs, organ procurement organizations, and histocompatibility laboratories joined UNOS to participate in the efficient and effective distribution of organs for transplantation.

The goals of UNOS, as outlined in the Articles of Incorporation, were to:

• Establish a national Organ Procurement and Transplantation Network under the Public Health Services Act;
• Improve the effectiveness of the nation’s renal and extra-renal organ procurement, distribution, and transplantation systems by increasing the availability of, and access to, donor organs for patients with end-stage organ failure;
• Develop, implement, and maintain quality assurance activities; and
• Systematically gather and analyze data and regularly publish the results of the national experience in organ procurement and preservation, tissue typing, and clinical organ transplantation.

The UNOS Board of Directors, composed of one representative from each member institution, governed the organization. UNOS and SEOPF remained closely intertwined, sharing office space, computer hardware, and personnel.

In 1986, UNOS sought and was awarded the federal contract to establish and operate the national Organ Procurement and Transplantation Network. With the awarding of the contract, UNOS changed its operation to accommodate the mandates of the law. In making the changes, UNOS sought input from the transplant community and its Board of Directors. UNOS also seriously considered the recommendations of the Task Force on Organ Transplantation. During the first year of operation as the national OPTN, UNOS enrolled new members and elected a new Board of Directors to conform with OPTN contract requirements. While the original Board of Directors consisted of a representative of each member, the new board included representatives of groups of members. As mandated by contract, the board was composed of 15 transplant surgeons and physicians and 16 non-physicians. Non-physicians were representatives of the following UNOS member categories: Independent Organ Procurement Agencies (two representatives), transplant coordinators (two representatives), Tissue Typing Laboratories (two representatives), Voluntary Health Organizations and Public Members (ten representatives). Public members represented the fields of ethics, law, religion, behavioral, and social sciences and included patients, patient advocates, and non-transplant physicians. Surgeons and physicians represented each of the ten UNOS
geographic regions (one each), and in addition included a President, Immediate Past President, Vice President, Treasurer, and Secretary (total = 15). UNOS later provided for a heart transplant representative to be elected to the Board of Directors, bringing the total number of board members to 32. In addition to enrolling members and creating a governing body, UNOS established an administrative organization with an executive director and assistant executive director and internal departments including: Technical Services and Computer Operations, Professional Education, Communications, Travel, Finance, Membership and Personnel. Later changes in the administrative organization included the addition of a Research and Policy Department with more specific responsibilities for supporting the scientific and policy-making functions of the OPTN.

For administrative purposes, UNOS divided the country into eight geographic regions. Due to size discrepancies and organ sharing concerns, several of the regions were altered to create a ninth, tenth, and eleventh region by the fall of 1989 (Fig. 1). Each region was assigned a UNOS staff administrator to assist in coordinating regional activities and to provide input to the UNOS committees and Board of Directors.

Also in the first year of operation, UNOS created 11 permanent standing committees: Communications, Education, Ethics, Finance, Foreign Relations, Transportation, Membership and Professional Standards, Heart Transplantation, Organ Procurement and Distribution, Histocompatibility and Scientific Advisory. An ad hoc committee on Patient Affairs was later made a permanent standing committee.

![UNOS Regional Map](image)
Ad hoc committees presently include Donations, Multiple Listing, Organ Procurement Organizations, and Pediatrics. Currently, committee members are recommended by the regional councilor and are selected to provide broad and experienced input into all committee activities. The president makes the appointment. Committees receive input from regional subcommittees, from the transplant community, and from the public. Each individual member of the OPTN is represented in all deliberations by the transplant organization or institution for whom he or she works.

UNOS established by-laws, membership criteria, and operating policies during its first year of operation. It also established a mechanism for public input into the policy-making process. Additionally, UNOS established a Scientific Registry under a two-year contract with the federal government. The Scientific Registry contains pre- and post-transplant data on all solid organ recipients in the United States as well as data on all donor referrals and actual organ donors.

Membership in the national OPTN was mandated in the Omnibus Budget Reconciliation Act of 1986. This legislation required that transplant centers be members of the OPTN and abide by its rules and policies or stop transplanting organs. If a transplant center elected not to join but to continued transplanting, that center would no longer be eligible to participate in the federal Medicare/Medicaid programs. As a result, membership in UNOS is no longer voluntary, and therefore policies set by UNOS govern all organ transplantation programs in the United States.

One of the provisions of NOTA in 1984 was that the Secretary of HHS would eventually submit a set of OPTN operating rules to the Federal Register; at that time, rules of the OPTN would acquire the force of law. The purpose of any set of rules would be as follows:

- The effectiveness of cadaveric organ procurement and distribution is improved;
- Access to an optimal organ transplant is improved and increased;
- The system for sharing renal and extra-renal organs is improved so as to:
  - Facilitate the matching of renal and extra-renal donor organs with potential recipients based on criteria established for each organ;
  - Provide a system by which highly immunologically pre-sensitized patients will be afforded the broadest possible opportunity to be matched with an acceptable donor;
- Improve transplant outcome; and
- Decrease organ wastage.
- Quality control is assured by collection, analysis, and publication of data on organ donation, procurement, and transplantation; and
- The professional skills of those involved in organ procurement and transplantation is maintained and improved.

In 1984, UNOS was incorporated as a legal entity, and in 1986, SEOPF gave it its computer matching system. The foundation also gave UNOS the 24-Alert voice-activated computerized matching system for non-renal vascular organs, developed for the North American Transplant Coordinators Organization in Pittsburgh.
UNOS received a contract from the federal government effective October 1, 1986, to put in place an organ procurement and transplant network. This network was to develop a national policy to assure equitable organ allocation. A point system developed through the University of Pittsburgh and later published in the New England Journal of Medicine was offered to UNOS by Dr. Thomas Starzl to be used nationally for allocating kidneys, livers, and thoracic organs. The UNOS Board of Directors adopted Dr. Starzl’s point system in May 1987 and implemented it on October 1, 1987, the date that the Organ Procurement and Transplant Network (OPTN) became operational.

In June 1988, the Board of Directors approved an allocation system for hearts and heart-lung combinations. This new system was not based on points, but instead allocated organs first locally, then to recipients within a 500-mile radius of the donor hospital, followed by recipients within a 500-1,000 mile concentric circle, and then finally, to all recipients beyond a 100-mile radius. These organs were allocated first to Status I patients (those patients who were critically ill and in urgent need of a transplant), and secondly, to Status II patients (all other potential heart recipients). (See UNOS Policy 3.7.) That policy went into effect January 4, 1989. At the February 1989 Board Meeting, the Board of Directors approved a modification of the point system for renal allocation that put a higher emphasis on antigen matching while maintaining a major emphasis on the length of time potential recipients had been waiting. Additionally, the new match process only considered the percent reactive antibodies of the recipient if the level exceeded 80 percent reactive antibodies and a preliminary negative crossmatch was available (see Policy 3.5). A simple pancreas allocation policy was developed in 1989 (Policy 3.6.10). Also in 1989, a slight modification was made to the liver allocation policy found in section 3.6 of the policies. The current organ allocation policy for each organ follows this chapter.

THE ORGAN CENTER

In 1982, the UNOS Organ Center was developed by SEOPF through a grant from the American Kidney Fund. The Organ Center was established to assist organ procurement coordinators with organ placement according to established protocols and to arrange transportation for those organs to the recipient center. The Organ Center is staffed 24 hours a day with trained personnel to help assure that organs are allocated, shipped, and delivered in a timely and appropriate fashion so that more patients can be transplanted with suitable organs. The Organ Center maintains the minimum acceptance criteria that each United States center uses for sharing organs. This information is updated periodically to be of the most benefit.

The Organ Center is used by most of the nation’s transplant centers and organ procurement organizations for sharing kidneys. Organ Center personnel receive the information from the donor center, access the computer for matches, and telephone potential recipient transplant centers and organ procurement organizations until they find a transplant center willing to accept the organ. Once they have identified the center, Organ Center personnel hook up a three-way telephone conversation between the donor center, the Organ Center, and the recipient
Organ Allocation in the United States

transplant center. This assures a clear understanding of the expectations by all parties. Next, the Organ Center arranges transportation from the donor center.

**ALLOCATION OF ABDOMINAL ORGANS**

**Kidney Allocation**

Kidneys are allocated on a local, regional, and national basis with the exception of mandatory sharing of six antigen matched kidneys. The allocation of cadaveric kidneys is made at the local level according to a point system. Patients on the local waiting list are offered kidneys in descending sequence with the patient with the highest number of points receiving the highest priority. A local area is defined by either the individual transplant center recipient list or a shared list of recipients within a defined procurement area which can be no larger than the OPO and service area designated by HCFA. The point system includes blood group, time of waiting, quality of antigen match, panel reactive antibody, and pediatric status. Medical urgency is not considered for kidney or pancreas allocation. A pay back system to the OPO of origin exists for six antigen match shared kidneys.

**Pancreas/Kidney Allocation**

Combined kidney/pancreas transplants are typically allocated according to the kidney allocation policies.

**Liver Allocation**

Organs are offered on a local, regional, and national basis. A point system similarly exists which includes blood group, time waiting, and degree of medical urgency. For every potential liver recipient, the acceptable donor size is determined and used as preliminary stratification.

Upon approval of the OPTN Board of Directors, a transplant center or an OPO may assign to each of the point systems’ criteria, points other than the number of points set forth by OPTN policy. In 2000 UNOS adopted the Model for End-stage Liver Disease (MELD) system for predicting the prognosis of patients with end-stage liver disease. The score relies on three laboratory parameters, bilirubin, prothrombin time (INR) and creatinine. A modification of the MELD system known as PELD has been adopted for allocating cadaveric livers to children. Both systems have been modified to take into account the patient with hepatocellular carcinoma, which can spread before bilirubin, prothrombin time and creatinine rise. Most agree that the new system is an improvement over the previous one, which depended heavily on waiting time, subjective prediction that death was likely within 7 days, and hospitalization in an intensive care unit.

**Increasing Disparity Between Organ Supply and Waiting Lists**

The past ten years have witnessed remarkable progress. Outcomes are vastly improved; the number of transplant centers has increased so that they are available throughout the country (over 100 centers each for heart, liver, and pancreas, 250 centers for kidney, 25 centers for lung, and 15 centers for intestine); large numbers of transplant physicians and surgeons have been trained; the waiting list
for all organ approaches 90,000 individuals; yet the number of cadaver donors has stalled at approximately 6000 each year. Many die each year while waiting for an organ transplant.

Because supply and demand are so far out of balance, consensus on fairness and utility in allocation algorithms is increasingly more difficult to achieve. Vocal articulate advocates of particular points of view have lobbied Congress and HHS for changes in the allocation rules. Dramatic stories in newspapers, magazines, and television have become commonplace.

RECENT DEVELOPMENTS

In 2000 the Secretary appointed a committee of 40 members to serve as an Advisory Committee on Transplantation. The Advisory Committee convened in November 2002 at the Secretary’s request to consider issues related to well-being of living donors, shortage of cadaveric donors and equal access to organ transplantation. The Advisory Committee made nine recommendations designed to increase cadaveric organ donation, two recommendations to encourage equal access to minority populations and seven recommendations with respect to living donors. All eighteen of the Advisory Committee’s recommendations are presented in Chapter 1 as part of a general review of long waiting lists and the increasing importance of living organ donors. Transplant related initiatives of the 2003 U.S. Congress and Senate are also part of that review.
INTRODUCTION

Organ procurement organizations (OPOs) are entities that play an integral role in the organ transplantation process through the provision of all activities related to organ donation. This includes education of the general public, education of medical professionals in hospitals, assisting hospitals with the development of written policies and procedures, obtaining family consent, medical evaluation of potential donors, the surgical removal of organs, organ preservation, organ distribution, and follow-up with participants of the recovery process. The OPO is also responsible for required reporting to the national Organ Procurement and Transplantation Network (OPTN), the Center for Medicare and Medicaid Services (CMS) and, in some cases, state health organizations.

Initially, OPOs were formed within academic transplant hospitals, typically in the department of surgery, to support the hospital’s kidney transplant program. In the late 1960s and early 1970s, a few of these entities formed their own governing structures and separated from the transplant hospitals to form independent, not-for-profit corporations. As more OPOs began operating as separate corporations, several bonded together to form a trade association, the Association of Independent Organ Procurement Agencies (AIOPA). This organization has evolved to include independent and hospital-based OPOs and is now the Association of Organ Procurement Organizations (AOPO).

Through the 1970s and midway through the 1980s, OPOs were essentially unregulated. Typically organ allocation occurred only locally and was at the direction of the transplant program(s). Organ sharing beyond the local programs was driven by expediency and, to some extent, medical priority. Early efforts to allocate organs via a structured system were coordinated through various organizations including individual OPOs, the Southeastern Organ Procurement Foundation (SEOPF) and the North American Transplant Coordinators Organization (NATCO). Authorized by the National Organ Transplant Act of 1984, the United Network for Organ Sharing (UNOS) currently holds a federal contract to be the OPTN. In recent years, UNOS has established and now oversees the national organ sharing system. All OPOs are required to be members of the OPTN.

During the development of the National Organ Transplant Act and shortly after its passage, there was a substantial shift from hospital-based OPOs to independent OPOs. Another remarkable effect of the legislation was a striking reduction in the number of OPOs. Currently, OPOs are regulated in terms of governance, function and performance. As reporting requirements have increased, so have

performance expectations. Most OPOs now expend significant resources promoting organ donation initiatives through public, professional and legislative avenues.

**LEGISLATION AND REGULATION**

Although organ procurement rates experienced moderate, but steady, growth during the 1970s and early 1980s, the growth rate of the transplant waiting list was much larger. The gap between supply and demand caused patient groups to insist on a fair system of organ allocation that would provide equitable access to organs on a national level. Legislators responding to their constituents rushed to introduce bills to deal with this issue. Among the numerous legislators participating in this effort were Senators Ted Kennedy, Orin Hatch and Dan Quayle, and Representatives Dan Marriott, Edward Madigan and Henry Waxman. However, a bill introduced in 1983 by a Tennessee Democrat, Congressman Al Gore, ultimately changed the face of history with respect to organ procurement and transplantation. After several days of hearings, Congressman Gore drafted legislation in October 1983 titled the National Organ Transplant Act. The bill underwent numerous revisions until it was passed into law on October 19, 1984.

The National Organ Transplant Act was an amendment to the Public Health Service Act and it was a landmark statute for the transplant world. Most other federal legislation that followed has been tied to this important law. The law was divided into four parts—Titles I-IV. Title I established a task force charged with examining issues related to human organ procurement and transplantation, making an assessment of immunosuppressive medications used in transplantation, and presenting a report to the Secretary of the Department of Health and Human Services (DHHS). The task force held its first meeting in February 1985 and submitted its final report in April 1986. The task force outlined 60 recommendations in its 232-page published report. Table 1 lists several of the recommendations that directly affected OPOs.

Title II of the act dealt with organ procurement activities. Section 371 defined OPO qualifications including non-profit status, service area size, board composition and functional capabilities. Regulations regarding OPO qualifications have been revised several times, and current regulations will be addressed later in this

<table>
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<th>Table 1. Task force recommendations affecting OPOs</th>
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<td>◊ The enactment of uniform state laws for the determination of death</td>
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<td>◊ The enactment of legislation requiring implementation of policies on organ donation and required request</td>
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<td>◊ The development of minimum performance standards for OPOs</td>
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<td>◊ Public education on organ donation targeted to minority populations</td>
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<td>◊ Incorporation of organ procurement and transplantation into the curriculum of nursing and medical schools</td>
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<td>◊ Certification of organ procurement specialists</td>
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<td>◊ Certification of not more than one OPO in any one service area</td>
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<td>◊ OPO governance similar to that described for the OPTN</td>
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<td>◊ A single national system for organ sharing</td>
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Organ Procurement Organizations

Chapter. Section 372 established the OPTN. The law provided initial funding for establishment and operation of the OPTN and set forth its qualifications, functions and board composition. Section 373 established a scientific registry to be awarded either by grant or contract. This registry was to include information on transplant outcomes. It was intended to allow patients and professionals to evaluate the scientific and clinical status of organ transplantation on an on-going basis. It has subsequently become the primary source of information for transplant patients to evaluate organ-specific outcomes at individual transplant centers. Section 375 of Title II established the Office of Organ Transplantation. This office was to coordinate organ procurement activities under Title XVIII of the Social Security Act (Medicare), conduct public education about organ donation, provide technical assistance to OPOs, and provide an annual report to Congress on the status of organ donation. The Office of Organ Transplantation was later made

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<th>Table 2. Summary of qualification requirements for OPO designation</th>
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<tr>
<td>◊ Must qualify as a nonprofit entity</td>
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<td>◊ Must have accounting procedures sufficient to maintain fiscal stability and to obtain payments from transplant centers for organs provided</td>
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<td>◊ Must have an agreement with the Secretary of DHHS for Medicare reimbursement</td>
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<td>◊ Must have an appropriately defined service area</td>
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<td>◊ Must have a director and sufficient staff to be effective in recovering organs from the OPO’s service area</td>
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<td>◊ Must have a Board of Directors with authority to recommend donation policy and which meets composition requirements defined in these regulations</td>
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<td>◊ Must have a documented working relationship to identify potential organ donors with at least 75% of the hospitals that have organ recovery capabilities and which participate in the Medicare and Medicaid programs</td>
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<td>◊ Must have a systematic approach to identifying potential donors and acquiring all usable organs from those potential donors</td>
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<td>◊ Must have a Board of Directors with authority to recommend donation policy and which meets composition requirements defined in these regulations</td>
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<tr>
<td>◊ Must have a system for allocating organs equitably in compliance with OPTN rules and with CDC Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissue and Organs</td>
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<td>◊ Must arrange for transportation of donated organs to transplant centers</td>
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<td>◊ Must coordinate its activities with area transplant centers</td>
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<td>◊ Must have cooperative arrangements with tissue banks</td>
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<td>◊ Must maintain data which demonstrates compliance with performance standards</td>
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<td>◊ Must maintain data and records in a format which could be easily transferred to a successor OPO to facilitate uninterrupted service</td>
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<td>◊ Must have procedures to assure confidentiality of patient records</td>
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<td>◊ Must conduct professional education</td>
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<td>◊ Must ensure that donor screening is performed by an appropriately certified laboratory to comply with OPTN standards and CDC screening guidelines</td>
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<td>◊ Must assist hospitals in making routine inquiries about organ donation</td>
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<td>◊ Must ensure that donors are tested for HIV markers in compliance with CDC guidelines and OPTN rules</td>
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<tr>
<td>◊ Must provide in a timely manner annual data concerning the population of the OPO’s service area, the number of actual donors, and the number of renal and extra-renal organs procured and transplanted</td>
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Liver and Intestinal Transplantation

a permanent part of the federal government when it was designated as a division under the Health Resources and Services Administration (HRSA). It is now referred to as the Division of Transplantation (DOT) and has taken on the role of overseeing the OPTN contract.

Title III of the National Organ Transplant Act made it unlawful for any person to transfer any human organ for valuable consideration if the transfer affects interstate commerce. The term “valuable consideration” did not include reasonable reimbursement costs associated with the acquisition, preservation and transportation of organs acquired from deceased donors. Title IV dealt with the establishment of a national bone marrow registry.

The Omnibus Budget Reconciliation Act (OBRA) of 1986 defined the requirement that each OPO be certified by Medicare as a qualified OPO. The law further stated that OPOs be re-certified every two years by meeting qualifying criteria and performance standards established by the Secretary of the DHHS. It quickly became evident that numerous OPOs would not qualify under the initial qualifying criteria, especially those criteria related to the size of the OPO’s service area and its donor potential. The ability of an OPO to qualify for certification was critical to its very survival. Any OPO not certified by October 1, 1987, would no longer receive payment for Medicare and Medicaid reimbursable expenses. As the deadline for certification drew near, OPOs across the country were merging and consolidating in order to meet the requirements. By the time the first certification process was completed, the number of OPOs had been reduced by approximately 40%.

Regulations related to OPO qualifying criteria and performance standards have been revised several times since 1986 and were last modified in November 2000. CMS still has not provided details about all elements of the new regulations, although one key element is the change in the certification cycle for OPOs from two to four years. The following are several key elements of the regulations used previously:

For an OPO to receive Medicare and Medicaid reimbursement, it must be exclusively designated by CMS to operate in a defined service area. To be the designated OPO for a service area, the OPO must make application to CMS and meet certain requirements including the following:

• The OPO must be certified as a qualified OPO and must be a member of the OPTN.
• The OPO must have a formal agreement with CMS for reimbursement.
• The OPO must have working relationships with hospitals and transplant centers within its service area.
• The OPO must provide cost projections and cost reports to CMS to establish reimbursement rates and must provide data to CMS related to organ recovery activity.
• The OPO must also comply with defined performance standards in order to be redesignated.
• The OPO must provide extensive information regarding its service area, including the size and boundaries, the population, names of the counties, and names of the hospitals with organ recovery capabilities.
A summarized list of designation requirements is shown in Table 2. The governing Boards of OPOs are also subject to composition requirements defined by the regulations. Table 3 lists the required member categories for an OPO’s Board of Directors. Although an OPO may have more than one board, at least one of the boards must be composed in accordance with the regulations.

Performance standards for OPOs were less stringent prior to January 1, 1996. To meet those standards, each OPO had to demonstrate that it procured from its service area at least 23 kidneys per million population per year and that, of those procured kidneys, at least 19 per million population per year were transplanted.

The current performance standards implemented January 1, 1996, include five performance categories: (1) number of actual donors per million population; (2) number of kidneys recovered per million population; (3) number of extra-renal organs recovered per million population; (4) number of kidneys transplanted per million population; and (5) number of extra-renal organs transplanted per million population. To be redesignated, each OPO must achieve at least 75% of the national mean in four out of the five performance categories per year averaged over the two years prior to redesignation. In theory, all existing OPOs could meet these requirements without any being closed. However, several OPOs have already failed to meet these standards and have been closed. It is anticipated that as the lower-performing OPOs drop out via the redesignation process, the performance mean will continue to rise. On the positive side, a rising mean accomplishes the objective of having mandatory performance standards by raising the overall performance requirements of OPOs. On the other hand, some OPOs will fail and there is no guarantee that there will be an improvement of performance in a given service area with a different OPO. There are many who argue that the current performance standards are inappropriate because they are based solely on population and don’t take into account population density, population demographics, trauma referral patterns or other factors that may influence organ donation activity but may be out of the sphere of control of the OPO. The AOPO and others who have criticized the validity of these standards are reviewing alternative standards that may more directly measure OPO performance. It is hoped that once CMS finally publishes the details of its November 2000 regulations, they will address the inadequacies of the January 1, 1996, performance standards.

The regulations also have a direct effect on hospitals. Each donor hospital in the OPO’s service area must have an agreement to work with the OPO designated for the service area in which the hospital is located. The hospital may request a

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**Table 3. Summary of requirements for OPO board composition**

◊ Hospital administrators, tissue banks, voluntary health associations and either intensive care or emergency room personnel within the OPO’s service area
◊ General public residing in the OPO’s service area
◊ A physician or individual with a doctorate degree in the biological sciences who is a specialist in histocompatibility
◊ A physician who is a neurosurgeon or a specialist in neurology
◊ A transplant surgeon from each transplant center affiliated with the OPO
waiver to work with a different OPO but must demonstrate that the waiver will
improve the rate of organ donation and ensure equitable access to recovered organs.

The regulations also deal with terminations of OPO agreements with CMS. OPOs may terminate voluntarily or involuntarily. If the OPO fails to meet the
definitions of CMS. OPOs may terminate voluntarily or involuntarily. If the OPO fails to meet the
performance standards described above, CMS may terminate its agreement with
the OPO. An OPO’s agreement with CMS also may be terminated immediately if
CMS determines the OPO is guilty of unsound practices.

A hospital-specific Medicare regulation implemented in August 1998 had a di-
rect impact on OPO operations. All Medicare-certified hospitals must comply
with this regulation or risk losing their agreements for Medicare reimbursements.
These hospitals must have written agreements with a designated OPO and at least
one eye bank and one tissue bank.

They must notify the OPO or the OPO’s designated third party of all deaths or
imminent deaths in the hospital. It is then the responsibility of the OPO to deter-
mine whether or not the individual is medically suitable for organ donation. It is
also the responsibility of the OPO or a designated requestor trained by the OPO
to discuss organ, tissue and eye donation with the family and obtain the appropriate
consent documentation. The regulation also requires hospitals to educate their
staffs about organ, tissue and eye donation issues, including identification of do-
nors and maintenance until the recovery can occur.

Previously, hospitals in most states only called the OPO about potential
donors. Criteria for such determinations were provided by the OPO. In reality,
most OPOs were being notified about a small percentage of the total number of

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Fig. 1. Organ supply vs. demand. Source: United Network for Organ Sharing
deaths in each hospital. The regulation placed a substantial burden on OPOs and hospitals. A direct impact on the OPO’s level of staffing required to handle donor referrals and subsequent donations occurred, and many OPOs found it necessary to expand their telecommunications and information systems capabilities as the level of referral activity increased.

**OPO Functions**

In the late 1960s and early 1970s, OPOs were often located in academic hospitals as programs within the hospital’s Department of Surgery or Transplantation. The organ procurement functions of those OPOs were typically limited to assisting in the operating room with kidney recoveries, kidney preservation, and transporting kidneys to neighboring transplant centers if they could not be used locally. At that time, kidneys were preserved almost exclusively by continuous pulsatile preservation. The job of the early procurement coordinators was usually more technical than clinical. The OPO’s employees were often technicians, seldom nurses, and almost never business people. It was very common for OPO staff members to have other responsibilities in the hospital or department in which they were employed. Often they were research technicians, dialysis nurses or technicians, heart pump technicians, or operating room nurses or technicians.

Since the mid-1980s, the overwhelming majority of OPOs have become independent of hospitals. The number of hospital-based OPOs still in existence today is very small and often function in a manner similar to independent OPOs. There are, however, a few ways in which hospital-based OPOs differ from independent OPOs. Independent OPOs are self-supporting, nonprofit corporations. Hospital-based OPOs may have segregated finances, but they are still financially tied to a hospital. The hospital-based OPO’s finances are reported as part of the hospital’s financial reports. The insurance umbrella of the hospital or university typically covers the hospital-based OPO, whereas independent OPOs must obtain their own insurance policies. Employees of hospital-based OPOs are really hospital employees and are subject to the hospital’s employment policies. Independent OPOs are companies that have anywhere from a handful to more than 150 employees; many have fewer than 30. Independent OPOs must adhere to state and federal employment laws, and most hire human resource consultants to ensure compliance. A number of OPOs have even hired full-time human resources personnel.

Most independent OPOs rent office space at one or more locations within their service area. A number have purchased their own buildings. Staffing has evolved to the point where many OPOs have departments including procurement, marketing, education, hospital development, human resources, information systems, accounting and others. Registered nurses and degreed nurses dominate the procurement staffs. Directors of OPOs, who had previously been clinical staff promoted from within, are increasingly becoming business or hospital executives hired from outside. Most OPOs have full-time accountants, and many now have full-time information systems specialists. As the focus on public and professional education has increased, most OPOs have hired marketing or education specialists. The annual operating budget of some of the larger OPOs is in the tens of millions of dollars.
Not only do OPOs look like serious corporations, they also act like serious corporations. Concepts such as strategic planning and strict adherence to employment laws that have long been commonplace in corporate America are now common in OPOs. Well-established OPOs have formal in-house training programs, employee handbooks, policies for compliance with environmental and health safety standards, internal performance standards and overall sound business practices.

The primary purpose of OPOs is to coordinate all aspects of organ donation and to maximize the recovery of usable organs for transplantation. This involves many functions beginning with public and professional education, media relations, hospital relations, tissue and eye bank relations, donor evaluation, family counseling and consent, medical management of the donor, and the surgical removal of organs. Additionally, OPO employees are responsible for organ preservation, organ distribution, transportation of organs, follow-up to donor families and medical staff, accounting and reporting, and contributing to industry knowledge. Add to that interpreting organ allocation policies, acting as a liaison between multiple surgical recovery teams and hospital staff, and ensuring compliance with all federal, state, OPTN, OPO, and hospital policies. The staff members of OPOs must juggle numerous medical, ethical, political and regulatory issues simultaneously, and they must do so under intense public, professional and regulatory scrutiny. It is not surprising that the burnout rate for OPO staff, especially clinical coordinators, is extremely high. An important OPO task is to develop employment screening techniques, training programs and retention programs aimed at maintaining adequate staffing experience and staffing levels.

Promoting donation is a key function of OPOs that have recognized that their operations are not driven by organ recovery, but that organ recovery is a result of effective marketing and education. OPOs are motivated by numerous factors to play a leading role in improving the rate of organ donation. Public interest is one of the motivating factors. Although there has been steady, but modest, growth in the number of organs recovered from deceased donors each year, the percent of increase has flattened since 1995. From 1988 to 1994, the number of organs recovered increased an average of 9.1% per year; from 1995 through 2002, the average annual growth was only 1.8%. Even more disturbing is the fact that the transplant waiting list is expanding at a much more rapid rate and shows no signs of slowing. In fact, the average annual increase in the size of the waiting list at year end from 1988 through 2002 was 28.6%. Additionally, OPOs are subject to intense pressure from affiliated transplant programs to provide organs for their patients. The third factor that motivates OPOs to increase the rate of donation is survival. Simply stated, OPOs that fail to meet government-imposed performance standards will be shut down.

In order to impact organ donation rates, OPOs must attempt to modify the attitudes and behaviors of the general public and medical professionals regarding organ donation. According to a survey conducted by the Gallup Organization, while 85% of the public claims to support organ donation, only 28% have signed a license or donor card indicating their intent to donate. Actual consent rates
further demonstrate the discrepancy between the stated attitudes of Americans toward donation and their actual behavior. According to the Partnership for Organ Donation, the rate of refusal to consent to donation was 50% in its study group. Assuming that study reflects national behaviors, one out of every two Americans asked to donate refuses. Many OPOs and others are focusing efforts to improve the consent rate through education about organ donation and by encouraging individuals to discuss their wishes to donate with their families. Groups within the general public that have particularly high refusal rates are being studied to determine what factors cause them to refuse to donate. As more is learned about the reasons for refusal, these groups are being targeted for focused education campaigns. Many OPOs have employed full-time staff specifically to coordinate public education campaigns. Interaction with the mass media, which had once been only reactive, is now a primary tool of public education for OPOs. In many OPOs, full-time public relations staff plan media events and work steadfastly to develop relationships with key media representatives in their service areas. This not only facilitates a more proactive approach to media involvement, but also creates a less adversarial environment when difficult news stories arise.

Although public attitude is the most significant determinant of organ donation activity, the attitudes of medical professionals also have a profound impact. A study by the Partnership for Organ Donation revealed that only one third of potential donors in hospitals actually became donors. Twenty-seven percent of the potential donors were either not identified or the family was not asked to donate, while the remaining third refused donation when asked. Although OPOs expend significant resources to develop strong relationships with hospital personnel, there is still a lack of participation among many medical professionals. Some of this can be attributed to personal feelings about donation, some to a lack of clear procedures, and some to a workload that causes them to view donation as a low priority. Virtually all OPOs have marketing or hospital development staff to work closely with hospitals toward an objective of improved participation. In some OPOs, the marketing staff is as large or larger than the clinical staff. These individuals facilitate the donation process by endeavoring to make a seemingly complicated process as simple as possible. They help the hospitals develop written policies and procedures, they provide around-the-clock in-service education programs, they provide role-playing opportunities, and they conduct postrecovery debriefing conferences. Some OPOs even provide debriefing sessions in situations when a referral does not result in a donation. Marketing personnel provide one-on-one support and recognition for hospital employees who participate in the organ donation process. Many OPOs also host annual conferences for nurses and physicians in their service area.

One of the most important activities of the marketing staff is to determine the annual donor potential in every donor hospital in the OPO’s service area. This is actually one of the best methods for an OPO to evaluate its own performance, and it is critical to resource planning. If an OPO can identify which hospitals have the highest donor potential, it can focus more of its resources toward those hospitals. Further, if the OPO can determine which hospitals are falling short of
their potential, it can reallocate its resources to improve performance in those hospitals. Knowing this information creates an opening for OPOs to give direct feedback to hospital administrators about the level of donor potential versus actual recoveries for any given period. The mechanisms for determining donor potential vary, but most involve some sort of retrospective review of medical records. Each OPO utilizes the methodology and criteria for donor suitability that best meet local needs. While this may be useful on a local level, the lack of consistency makes it impossible to determine donor potential at the national level. Beginning in 1997, the AOPO conducted a pilot project designed to develop a methodology for estimating organ donor potential. A secondary motive of this project was to provide the data necessary to develop better national performance standards based on true donor potential rather than the current standards that are based on population. There have been many estimates of the national donor potential calculated by numerous methods involving extrapolation. The AOPO Death Record Review study recently projected the national donor potential at 11,000 to 14,000 potential donors per year.

Relationships with eye and tissue banks can have a direct impact on the performance of an OPO. By association, medical professionals and members of the general public often assume that the OPO, the eye bank and the tissue bank are a single entity. While in some cases this may be true, it most frequently is not. It is important for these three entities to coordinate education programs, donor referrals and recoveries to provide the smoothest possible procurement service to donor hospitals. Any complications in the process that can be attributed to poor communications between OPOs, eye banks and tissue banks can create a risk that hospital participants or public attitudes will be compromised. It is the responsibility of OPOs to take the lead in coordinating the activities of the three entities since it is mandated that all hospital deaths must be reported to the OPO.

THE ORGAN PROCUREMENT PROCESS

Virtually all OPOs recover multiple organs from donors, whenever possible. Additionally, some OPOs also recover eyes and tissues. It is the responsibility of the OPO to initially evaluate potential donors for medical suitability. This requires the clinical coordinators to have extensive medical knowledge about the physiology and function of multiple organ and tissue systems. The coordinators must be skilled at reviewing, sometimes voluminous, medical records for pertinent information that may provide insight about organ function or that may identify contraindications to donation. Coordinators also must be resourceful in determining past medical history and high-risk behaviors. This information is obtained through previous hospital admissions, as well as discussions with nurses, attending and family physicians, and friends and family members. Obviously, the coordinators must exercise the utmost sensitivity when discussing these issues with family members and friends.

Clinical coordinators and other staff receive specific training in counseling grieving family members about the organ donation process. Some OPOs also train designated requestors, who typically are hospital employees. This is especially
important in situations where the hospital is located a significant distance from
the OPO. It is imperative that the families of potential donors are approached
regarding the option of donation with compassion and sensitivity, recognizing
the sudden loss of their loved one. As noted previously in this chapter, OPOs are
required either to speak directly to the family about consent for donation or they
must be involved by training a designated requestor. Many past studies have shown
that personnel from OPOs are more effective than nurses, physicians or hospital
clergy in securing consent. However, recent studies have demonstrated that the
consent rate is even higher when the discussion is conducted jointly by a member
of the OPO along with a member of the hospital staff. It is important that the
OPO coordinator provide complete information to the family about the donation
process, including the timeframe for completion. The coordinator also must pro-
vide updates to the family if there are unexpected delays. It is imperative that the
family not feel pressured or harassed. Their decision about donation should be
respected even if their answer is no. Coordinators must be cognizant of the criti-
cal balance between the desire to get consent for a given donation and the possible
ill will that could result from alienating a potential donor’s family.

Once a donor has been identified and the family has consented to donation, it
is critical that appropriate medical management is provided to ensure that the
organs are functioning optimally at the time of recovery. Before the OPO can
begin its involvement in medical management, death must be declared and docu-
mented appropriately in the donor’s medical record. The first step in the donor
management process is to determine the current status of organ function. This is
accomplished by physical examination, review of past and current medical records,
obtaining necessary laboratory tests and other diagnostic tests or consultations. A
detailed discussion of medical management of deceased organ donors is beyond
the scope of this chapter, but several key objectives are described as follows. Perfu-
sion and oxygenation are the two main goals of donor management. Maintenance
of normal blood pressure, fluid electrolytes and blood oxygen levels are the key
ingredients in accomplishing those objectives. In the process of managing the donor
to achieve optimal function of one organ, coordinators must be careful not to
compromise the function of another organ. For example, it is desirable to main-
tain a brisk diuresis in the kidneys up to the moment of surgical recovery. How-
ever, overhydrating a donor may cause excess fluid in the lungs and may
compromise pulmonary function. It is important for the medical management of
the donor to be performed in a manner consistent with the optimum function of
all transplantable organs.

The coordinators also are responsible for ordering laboratory tests to deter-
mine the presence of any transmissible diseases such as HIV, hepatitis or other
systemic infections. All OPOs have Medical Directors or physicians designated to
oversee and assist as necessary in the screening and medical management of do-
nors. Their level of involvement in a given case depends on the complexity of the
case and the experience level of the coordinator. Additionally, physicians from
each of the receiving transplant teams may request specific tests or management
parameters. It is the role of the coordinator of the host OPO to coordinate the
numerous variations that often occur with different recovery teams and be as responsive as possible to the needs of each. Of course, special requests must not interfere with sound donor management and should not be permitted to compromise one organ to the benefit of another.

After the evaluation and management of the donor is in progress, the coordinator must place the organs. The federal government, through the contracted OPTN, regulates organ allocation. Coordinators must register each donor with the OPTN, and allocation is determined through computer matching by the OPTN. Once a transplant center has accepted an organ, it is the responsibility of the coordinator from the host OPO to communicate with the coordinator from the receiving center to coordinate and schedule the surgical recovery. The host coordinator often assists in obtaining local transportation for a team flying in from a distant location. The coordinator also should determine and assist with any special needs of that team. In some situations, one team may be removing all organs. More typically, several teams are involved in each surgical procedure. The coordinator of the host OPO is responsible for coordinating the arrival of each team and discussing the order of the surgical procedure with members of the surgical teams.

Typically, each recovery team provides its own preservation fluids and supplies. The coordinators are responsible for preparing preservation solutions and making them available to the surgical recovery team at the appropriate time during the procedure. The length of warm and cold ischemic periods are important to the anticipated function of transplanted organs, and the coordinators are responsible for documenting when these periods begin and end. Other times, such as the incision time and the time of drug administration also are documented during the procedure. Although most organs are preserved by static cold storage, some OPOs preserve kidneys by continuous pulsatile perfusion. This requires special knowledge and technical skills including surgical skills and the operation of perfusion equipment. Each preservation method has its advantages and disadvantages, but both work well provided that the length of preservation is kept within acceptable parameters.

The coordinator for each recovery team is responsible for appropriate packing and labeling of organs, tissue typing materials, and any specimens that will accompany their organ(s). This must be done in strict compliance with OPTN policies to prevent errors and provide consistency. The receiving transplant center or laboratory may refuse organs or tissue samples that are not appropriately labeled. The OPO must have established relationships with histocompatibility laboratories for tissue typing and crossmatching. Ideally, blood or tissue samples are delivered to the histocompatibility laboratory prior to the start of the surgical recovery. However, in distant locations, it may not be practical or cost effective to arrange for prerecovery tissue typing. Lymph nodes, blood and other tissue samples are collected during the surgical recovery and the coordinator is responsible for arranging for those samples to be delivered to the histocompatibility laboratory.

Organs are transported in several ways. Sometimes they accompany the recovery team back to the transplant hospital; sometimes they are shipped by commercial or charter aircraft unaccompanied. In the case of pulsatile perfusion, the
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coordinator or perfusion technician attends to the machine whether the kidney is used locally or at a distant center.

Organ donation only occurs through the good will of the general public and the participation of the medical community. Successful OPOs do an effective job of following-up with members of the donor’s family, medical professionals and others who were involved in a given case. An organ recovery is an enormous event involving from 20 to 100 individuals. This includes all the immediate family members, nurses and physicians in the emergency room, ICU and operating room, hospital administrators, hospital security, transportation personnel and a host of others. Prompt feedback to each of these individuals is generally very meaningful to them. Letting them know how much they are appreciated and how much their efforts contributed to saving and improving the lives of others can motivate them to participate in the future. At the very least, it helps them to feel appreciated for participating in a process that can be very stressful and emotional. Typically the feedback is in the form of a letter, but it can also come in other ways. Appropriately timed phone calls to the family are sometimes helpful and provide an opening for the family members to ask any unanswered questions they may have regarding the process. De-briefing meetings with medical professionals have been shown to be an effective way to allow staff members to ask questions or simply vent their feelings. It is also the responsibility of the OPO to follow-up on blood cultures or any other laboratory tests that were not completed prior to the recovery and report the results to receiving transplant centers.

Organ transplantation is an effective, but expensive, treatment for end-stage organ failure. Organ acquisition is a significant component of the overall expense, with the procurement-related costs of some organs exceeding $25,000. The OPO bears the initial cost of organ acquisition and is reimbursed by the transplant center that receives the organ. The transplant center then recovers that cost directly from the patient or third party payer. For kidneys, the third party payer is usually Medicare. Since kidneys represent approximately half of the activity for most OPOs, a substantial portion of OPO funding comes from this source. In fact, OPOs are required to file an annual cost report with CMS. If the cost report indicates that the OPO charged more than its actual cost for kidneys, the OPO must pay that amount back to Medicare. Conversely, if the OPO undercharged for those organs, Medicare reimburses the OPO. Where kidney costs and reimbursements are concerned, the OPO must break even with Medicare for reimbursed expenses. Although the cost report is due annually, OPOs may file for an interim adjustment during the year if they can document a substantial loss.

In the case of kidneys, all OPOs charge transplant hospitals a standard acquisition charge. They create a cost center specifically for kidneys and track all expenses attributable to kidney acquisition over the course of a year. This includes direct expenses such as donor hospital charges and transportation, as well as indirect expenses such as professional education, salaries and rent. Direct expenses are relatively simple to identify, but indirect expenses can only be reimbursed by Medicare to the extent those expenses can be tied to kidney acquisition. A portion of salaries and other indirect expenses also are allocated to the acquisition of
extra-renal organs. Furthermore, Medicare has strict procedures for determining what expenses can be included in the kidney cost center. Once the OPO has established a financial history, it can accurately project expenses in an annual budget. The standard kidney acquisition fee is then calculated by dividing the projected kidney related expenses by the number of projected kidney transplants. Since this is only done at the beginning of each fiscal year, variations in actual versus projected costs can easily result.

Revenues that occur as a result of reimbursement for extra-renal organs are similar to reimbursement for kidneys; however, OPOs are not required to break even for extra-renal organs. As nonprofit entities, OPOs are allowed to build and maintain a fund balance, although no revenues in excess of actual cost can be acquired from kidney revenues. For many years, some OPOs operated with little or no cash reserves, which created serious difficulties in times of slow donor activity. As OPOs have become more sophisticated in their financial practices, they have realized that a strong fund balance is essential for the effective operation of their organizations. Many OPOs include financial planning as part of their annual strategic planning process. Although presently there is no industry standard, many OPOs are wisely building fund balances equal to several months of operating expenses. Unquestionably, OPOs are under intense public scrutiny to be cost effective. It is important for OPOs to expend their resources wisely and to avoid unnecessary expenses or anything the public might consider extravagant. However, it would be very fiscally irresponsible for an OPO to allow its cash reserves to diminish to a point that routine operations are compromised.

All OPOs must report their financial data to CMS annually. They also are subject to periodic financial audits by CMS. Additionally, most OPOs undergo independent financial audits. They must file a corporate tax return to the Internal Revenue Service. And, even though not required, most OPOs provide detailed information to affiliated transplant centers regarding the determination of their organ acquisition charges. In addition, OPOs have public board members that review their budgets and financial data.

In addition to financial reporting, OPOs also must comply with the data reporting requirements of the OPTN, various offices of the federal government and, in some cases, state government or health associations. OPOs must document and report organ recovery activity, compliance with federal OPO regulations, compliance with health and safety standards, compliance with OPTN membership standards, and compliance with OPTN allocation policies. Occasionally OPOs must respond to inquiries from the Office of the Inspector General and other governmental agencies. In some cases, state laws regarding donation have been enacted that require OPOs to report information to state or local health authorities. Affiliated hospitals certainly expect a high level of reporting from the OPO regarding organ recovery activity, marketing activity and finances.

Organ recovery productivity varies, sometimes dramatically, from one OPO to the next. It is in the public’s interest for all OPOs to perform at a high level. High-producing OPOs often demonstrate many innovative practices that have maximized their performance. Conversely, low-performing OPOs often identify unique
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and sometimes unavoidable areas that detract from their performance. An open exchange of information that contributes to the industry knowledge is healthy and beneficial to all OPOs. This can best be accomplished through active participation in trade associations such as AOPO or professional associations such as NATCO, verbal or poster presentations at national meetings, and the publishing of professional papers. Although most OPOs have developed a high level of technical expertise, no OPO has claimed to discover the secret to maximizing organ donation. There is no single magic formula for improved performance. Rather, this is best achieved through a host of activities that combine to affect the behavior of the public and the medical professionals. The extent to which an OPO can discover and implement effective techniques will ultimately determine its performance.

INITIATIVES TO INCREASE DONATION

Each year the gap between supply and demand for transplantable organs widens. Many initiatives to increase the supply of organs have been attempted, and new ones surface at a steady pace. Some of these are very localized and are undertaken by a single OPO. Some are statewide or regional and may be the work of coalitions between donation-related entities or may be the result of statewide legislation. There are numerous examples of national initiatives by associations, coalitions, congress, private corporations and others. The goal of each is the same, but the approach is usually varied. Some are designed to improve the consent rate, some are intended to motivate the public to donate, some are oriented toward expanding the medical acceptance criteria, and others are focused on improving the caliber of OPOs and their employees. Unfortunately, the overall success of these initiatives has not been dramatic, but combining several different approaches may ultimately yield measurable results.

The first notable initiative was the Uniform Anatomical Gift Act of 1968. This legislation, which has been adopted in some form by all states, described provisions to allow individuals or their immediate family members to legally give consent to allow their organs to be donated at the time of death. This legislation gave rise to the development of donor cards. Various campaigns promoting the use of donor cards have evolved including the placement of an individual’s donation status on the driver’s license in most states. Additionally, donor cards are available from many other sources. If appropriately executed, a donor card is considered a legal document.

Several other initiatives related to consent issues also have been implemented. The concept of required request was introduced in the 1980s by an ethicist, Arthur Caplan. This is a process whereby donor hospitals must present the option of donation to all potential donors in their hospitals. Required request was first attempted at the state level and eventually became a federal statute. There has been limited success reported with required request. Unfortunately, the definition of potential donor was left to the donor hospital and, in many cases, the option was not presented because the hospital prematurely or erroneously deemed an individual unsuitable for donation.
As described above, this concept was taken one step further with CMS regulations requiring hospitals to report all deaths to OPOs and with OPOs being responsible for determining donor suitability. Failure to comply with these regulations can cause a hospital to lose its Medicare and Medicaid funding. Although these federal regulations were based on a state law in Pennsylvania that reportedly resulted in a 40% increase in donation over a three-year period, the impact on organ donation nationally has been relatively modest. Recently, the concept of First-Person Consent legislation (also referred to as "Donation by Donor Designation") has been adopted by many states. First-Person Consent allows OPOs to recover organs from a person who signed up to be a donor through a registry or a uniform donor card, without the signature of two witnesses or consent from the next-of-kin.

Perhaps the last consent-related initiative is presumed consent. Although not currently practiced in the U.S., the premise of presumed consent is that all individuals are considered organ donors unless there is prior notice of objection to donation by the individual. The rationale for this thinking is that since public attitude polls have demonstrated that most people favor donation, it is safe to assume they are willing to donate unless they give notice to the contrary. This has been tried in other countries with some success, but there has been substantial reluctance to legislate it in the United States. Some states have passed limited presumed consent laws that typically permit donation of eyes or tissues unless there has been a prior notice of objection. In these situations, eyes and tissues are removed without consent from the next-of-kin. There has been limited success in increasing the rate of such donations, but there also have been situations where the family has reacted strongly to the donation that occurred without their consent.

Several local coalitions of OPOs, tissue banks, eye banks, transplant programs, voluntary health associations and other interested individuals have formed. The objective of these groups is to improve local donation rates through education and improved public awareness. There also have been formally organized national coalitions. The Coalition on Donation, formed in the mid 1990s, is a prominent national coalition active today. The objective of this group is to establish one unified national message about organ donation. It has developed donation awareness campaigns that have been widely utilized by OPOs and transplant programs across the country. Other national organizations and all OPOs conduct public education and donor awareness programs. It is difficult to empirically measure the effectiveness of these initiatives, but most agree they are very important and will prove helpful over time.

One of the provisions of the National Organ Transplant Act of 1984 is that buying or selling human organs is prohibited. However, there is an initiative, albeit controversial, to increase public participation in donation designed to induce individuals with financial incentives. These incentives take various forms with the most direct being a cash payment to the immediate next-of-kin of the donor. Others are less direct and include proposed payments for funeral expenses, tax deductions, donations to named charities, life insurance policies, and a plethora of other types of compensation. Proponents argue that everyone benefits from
organ transplantation except the donor; therefore the donor’s family should be reasonably compensated. They also argue that it is logical to think that more people will be motivated to donate if they are paid than if they are not. Opponents argue that removing altruism will prey on those in lower socioeconomic positions and may actually reduce the donor pool. There is also a concern that family members may be less than forthright about the donor’s medical history when tempted with compensation for the donation. Public opinion polls and focus groups have demonstrated a lack of enthusiasm for financial incentives, and some individuals have stated they would not participate for reasons other than altruism. Whether or not financial incentives would increase donation remains to be seen. However the biggest obstacle to financial incentives must be addressed before they can even be tested. One of the provisions of the National Organ Transplant Act of 1984 is that buying or selling human organs is prohibited.

A number of medically oriented initiatives have been attempted to increase the availability of donor organs. For example, in the late 1980s surgeons from Loma Linda University Medical Center began a series of transplants utilizing organs recovered from anencephalic infants. As they and others explored this possible source of donor organs, they encountered a number of obstacles. First, determination and declaration of brain death in anencephalics does not fit traditional guidelines. Second, in 1989 the UNOS Board of Directors endorsed a policy developed by its ethics committee discouraging the use of anencephalic infants as donors. Third, the results of transplants from anencephalic donors were poor when compared to organs recovered from traditional organ donors. The use of anencephalic infants as organ donors has become essentially nonexistent in recent years.

One fairly successful approach to increasing the organ supply has been to broaden the criteria for donor acceptance, but only to the extent that donation can occur without negatively impacting transplant outcomes. As transplantation technology has evolved, transplant physicians have discovered that donor organs that had previously been considered unacceptable are often quite suitable for transplantation. It is not surprising that as donor management and post-transplant care of the recipient have improved, so has the ability to use organs from “expanded donors” a term coined by transplant professionals in the mid 1990s. There are many examples of expanded donors, and undoubtedly the list will continue to grow. Acceptance of organs from older donors, donors with some degree of hypertension, non-heartbeating donors, Hepatitis C positive donors, and other expanded donors all have been used effectively given the appropriate donor/patient circumstances. Some disagreement remains regarding acceptable donor criteria, but this approach has received much interest and has been proven effective in many centers.

Increasing donation by improving the proficiency of procurement personnel and the performance of OPOs has been an ongoing goal of procurement professionals. While it may be difficult to quantify the impact of this approach, its effect can only be positive. After several years of development, the American Board of Transplant Coordinators (ABTC) conducted its first certification exams in 1988. This voluntary certification is designed to measure competency for transplant
clinical coordinators and transplant procurement coordinators. A few years later, the AOPO instituted voluntary accreditation of OPOs. Members of its Accreditation Committee conduct a site visit with each OPO seeking accreditation. They rigorously scrutinize all aspects of the OPO's operations and score them against standards that were developed by the AOPO. Many of the nation's OPOs have been accredited by the AOPO, while others are actively pursuing accreditation.

In 1996, the AOPO completed its first financial benchmark process for its participating members. This was a comprehensive analysis of OPO finances. The objective was to provide to each OPO a comparison of the finances of similar OPOs. National statistics also were made available to participants and presented to members of the association at its annual meeting. The concept was to share information that would allow OPOs to determine whether or not they were allocating resources in a manner that would result in high performance. For example, if a low-performing OPO determines that it allocated a substantially lower percentage of its resources to marketing than did higher-performing OPOs, it may adjust that allocation accordingly. Simply stated, this is a process that can help to reveal best financial practices with the hope of improving the overall performance of participating OPOs.

**DISCUSSION**

Thousand of patients each year receive organs supplied by the nation's OPOs. Without the skill and commitment from the individuals who work in these OPOs, the number of transplant procedures occurring in the United States would be greatly diminished. The ability of OPOs to stimulate participation in organ donation is a key element in meeting the needs of those who are waiting for transplants. This is accomplished through sophisticated marketing and education, innovative practices, contributing to industry knowledge, relationship building, and expert public relations.

Many OPOs have developed a high level of expertise in marketing. Most practice market segmentation and target marketing, and most OPOs expend significant resources in this area. OPOs are constantly trying innovative techniques to improve performance. These range from advancing technology to improving the workplace environment to developing better techniques for stimulating public and professional participation in donation. Sharing information about their successes with these innovative practices is necessary to contribute to the industry knowledge base. This allows others to emulate best practices with an objective of improving overall performance of OPOs throughout the country. As with all successful organizations, OPOs have recognized the importance of effective networking at all levels. They spend a great deal of time building relationships in hospitals,
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with community leaders, with medical professionals, and among their peers. They also have focused attention on developing relationships with representatives of the news media. This helps to ensure fair reporting when negative news stories about procurement or transplantation arise. Although the transplant community is endeavoring to educate the public about these issues, the public generally is not adequately informed. This situation has added to the mistrust of OPOs and the donation process. Certainly, these problems will require the continued attention of OPOs and the entire transplant community.

Organ procurement is a very complicated process, often involving dozens of people. The primary objective of OPOs is to simplify the process by coordinating the countless tasks and communicating effectively with everyone involved. The extent to which OPOs can accomplish this objective will be paramount to the overall success of transplantation in the United States.

REFERENCES


5. Conditions of Participation for Hospitals. 42 CFR, §482, 1998. This regulation defines current hospital requirements for interacting with OPOs regarding identification and evaluation of potential organ donors. It also defines the mechanism for presenting the option of donation the potential donor’s family.


7. The Gallup Organization, Inc. The American public’s attitudes toward organ donation and transplantation. Boston, 1993. This is the most current national public opinion poll regarding organ donation.

Procurement and Short-Term Preservation of Cadaveric Organs

Anthony M. D’Alessandro and James H. Southard

ORGAN DONATION

Improvements in immunosuppression, organ preservation, surgical technique, as well as long-term recipient management have led to tremendous success following transplantation. Consequently, more patients than ever before have benefited from transplantation. Unfortunately, the rate of organ donation has not kept pace with the ever-increasing recipient waiting lists. Recent United Network for Organ Sharing (UNOS) statistics reveal that greater than 80,000 patients (Table 1) currently await transplantation. For a variety of reasons, some organ procurement organizations (OPOs) have very high organ donation rates while others fall significantly below average. Likewise, consent for organ donation averages approximately 60%, although several OPOs have much higher consent rates. Clearly, much greater emphasis needs to be placed on increasing organ donation. Organizations such as the Coalition on Organ Donation, the American Society of Transplant Surgeons (ASTS), UNOS, and the American Association of Organ Procurement Organizations (AOPO) are leading the way in this effort. Still a critical shortage of organs exists which has resulted in an increase in the use of live donation and an increase in the use of expanded cadaveric donors. Since criteria for the use of organs has expanded significantly, any patient who is declared brain dead or who is being withdrawn from support should be considered as an organ donor.

DETERMINATION OF DEATH

Patients may be declared dead by brain death criteria and by cardiopulmonary criteria. Currently, the majority of organ donors (98%) are declared dead by brain death. The definition of brain death was first examined in a report by the Harvard Medical School in 1968 and guidelines later set for brain death determination in 1981 which led to the “Uniform Determination of Death Act.” These criteria are shown in Table 2.

Brain death occurs when complete and irreversible loss of brain and brain stem function occurs, which presents clinically as complete apnea, brain stem areflexia, and cerebral unresponsiveness. In order to evaluate a patient clinically for brain death, several preconditions must be met. The patient must be on a ventilator in a coma and have a cause for underlying brain damage. Most cases are caused by trauma, subarachnoid hemorrhage, cerebral abscess or tumor, meningitis, encephalitis, or cerebral hypoxia. Reversible causes of brain stem depression such as hypothermia and drug intoxication must first be excluded. Trauma patients are
often intoxicated with alcohol. Thus, 8 hours should be allowed to pass if alcohol use is suspected before a diagnosis of clinical brain death can be made. Patients in intensive care units may also be under the influence of sedative or paralytic agents.

Clinical testing is relatively straightforward and examines the presence of brain stem reflexes and the presence of total apnea. Five brain stem reflexes should all be absent in order to diagnose brain stem death: pupillary response to light, corneal reflex to touch, vestibulo-ocular reflex using the cold caloric test, the gag reflex, and the apnea test. The apnea test demonstrates the absence of respiratory drive to PaCO2 greater than 50 mmHg. During apnea, the PaCO2 rises by about 2 mmHg/min; thus, if the starting PaCO2 is over 30, the PaCO2 will rise to over 50 mmHg in about 10 minutes. To prevent hypoxia during these 10 minutes, the patient should be preoxygenated prior to the test. Confirmatory studies, although not necessary, include serial electroencephalography and radionuclide scan to assess cerebral perfusion.

Death may also be declared by cardiopulmonary criteria, and in certain instances, particularly when patients are being withdrawn from support, organ donation is possible. This type of donation is referred to as donation after cardiac death (DCD) or non-heart-beating donation. Prior to the Harvard criteria defining brain death in 1968, all organ donors were DCD donors. Although some warm ischemia occurs in these donors, several centers have shown that renal and
Liver and Intestinal Transplantation

Extrarenal donation is possible. Recently the Institute of Medicine (IOM) reviewed non-heart-beating organ donation, published guidelines, and concluded that NHBDs are a medically and ethically acceptable source of donor organs. Currently, NHBDs comprise 2% of organ donors and this percentage will likely increase since the results of transplantation have been shown to be acceptable.

**EVALUATION AND SELECTION OF DONORS**

OPOs form a vital link between referring donor hospitals and transplant centers and should be notified as early as possible in order to make the determination of suitability for organ donation.

Obtaining consent for organ donation is of paramount importance in increasing organ donation. A caring sensitive approach by trained individuals that have time to spend with families cannot be overstated. Organ procurement personnel, clergy, and nursing staff play a vital role in this area. Once consent is obtained, a review of the patient’s history should focus on the mechanism of death, periods of hypotension or cardiac arrest, need for vasoactive medications, and previous surgery. Likewise, the patient’s social history, including alcohol and drug use, should be known. Generalized infectious diseases are ruled out by obtaining human immunodeficiency virus (HIV) antigen, anti-HIV-1, anti-HIV-2, human T-cell lymphototoxic virus (HTLV)-1 and HTLV-2, anti-cytomegalovirus (CMV), anti-hepatitis C virus (HCV), hepatitis B surface antigen (HBSAg) and hepatitis B core antibody. Specific organ function is primarily determined by laboratory data, chest x-ray, electrocardiogram, and echocardiogram.

Since criteria for organ donation are expanding, there are fewer absolute contraindications to organ donation (Table 3). Relative contraindications to organ donation have increased since many were previously considered to be absolute contraindications. Table 4 should be considered only as a guideline to relative contraindications since many centers have successfully utilized organs from every category listed.

As a general rule, hepatitis C positive donors may be used in hepatitis C positive recipients. Also, as long as hepatic trauma is minimal, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are decreasing, and macrovesicular steatosis is < 60%, the liver may be used. Hepatitis B core antibody positivity is more controversial, but with long-term hepatitis B immune globulin (HBIG) use, transplantation may be indicated depending on the clinical situation.

### Table 3. Absolute contraindications to cadaveric organ donation

<table>
<thead>
<tr>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>Malignancy outside central nervous system</td>
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<tr>
<td>Prolonged warm ischemia</td>
</tr>
<tr>
<td>Long-standing hypertension</td>
</tr>
<tr>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Intravenous drug abuse</td>
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<tr>
<td>Human immunodeficiency virus</td>
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</tbody>
</table>
One of the best indicators of whether or not a liver should be used is the intraoperative assessment of an experienced donor surgeon. This is also true for pancreas donors since glucose levels may be elevated due to exogenously administered glucose and steroids as well as to catecholamine release and insulin resistance from trauma. Likewise, an elevated serum amylase does not always reflect pancreatic trauma and should not in isolation be used to preclude pancreatic organ donation. A history of early renal disease, such as mild hypertension and diabetes, may also be compatible with organ donation. A renal biopsy can be obtained to assess the degree of pathology, if any, prior to transplantation. Likewise, in older donors, if glomerulosclerosis is present, both kidneys may be implanted. In children less than 6 years of age, and depending on size, the kidneys can be implanted separately or en bloc. Although heart and lung donor criteria are somewhat more restrictive, depending on the potential recipient’s condition, these criteria can be expanded. Cadaveric heart donors should have a normal chest x-ray, electrocardiogram, isoenzymes, and echocardiogram. Lung donors should not have any chest trauma and should have negative sputum cultures and a $\text{PaO}_2 \geq 350$ torr on an $\text{FiO}_2$ of 1.0. Again, examination of the organs by a skilled heart and lung donor surgeon may be necessary before excluding a potential donor.

Due to the risk of organ dysfunction and failure with increasing cold ischemia time, preservation times should be minimized to avoid exacerbating the current donor shortage. Safe acceptable cold ischemic times vary with each organ and, as a general rule, are as follows: heart/lung 6 hours, liver 12 hours, and pancreas 18 hours. Since delayed renal graft function predicts long-term survival, attempts should be made to limit preservation times. When kidneys are cold stored, they should be transplanted within 18-24 hours, and when machine-perfused within 24-30 hours.

### Table 4. Relative contraindications to organ donation by organ type

<table>
<thead>
<tr>
<th>Heart/Lung</th>
<th>Liver</th>
<th>Pancreas</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 50</td>
<td>Age &gt; 60</td>
<td>Age &gt; 55</td>
<td>Age &gt; 60; &lt; 6</td>
</tr>
<tr>
<td>High dose inotropes</td>
<td>Hepatic trauma</td>
<td>Amylase elevation</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Wall motion abnormalities</td>
<td>AST, ALT elevations</td>
<td>Glucose elevation</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Chest trauma</td>
<td>Hepatitis B core antibody</td>
<td>Fatty pancreas</td>
<td>ATN (creatinine $\geq 2.5$ mg/dL)</td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>Hepatitis C</td>
<td>Hepatitis C</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>$\text{PaO}_2 &lt; 350$ on $\text{FiO}_2$ 1.0</td>
<td>Steatosis</td>
<td>Prolonged warm and cold ischemia</td>
<td>Prolonged warm and cold ischemia</td>
</tr>
<tr>
<td>Prolonged cold ischemia</td>
<td>Prolonged warm and cold ischemia</td>
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THE EXPANDED DONOR

The expanded donor, previously referred to as the marginal donor, has assumed a much greater role in transplantation due to the critical shortage of organs. Prior to the waiting list reaching its current size, ideal donors were primarily utilized. Ideal donors are young, normotensive, brain-dead donors free of any disease and with minimal warm ischemia times. Table 4, which outlines the relative contraindications to transplantation may also be viewed as criteria that define the expanded donor. DCD donors, whether controlled or uncontrolled, should also be included in the expanded donor pool since warm ischemia times are greater and there are higher rates of delayed graft function. Likewise, split liver transplantation, where one donor liver is shared between one adult and one child or between two adults, should also be considered in the expanded donor definition.

However, what is important to consider when utilizing expanded donors is the risk of a patient dying on the waiting list versus the risk of dying with transplantation of an organ from an expanded donor. Although graft function may initially be worse and long-term patient and graft survival less than from organs transplanted from ideal donors, the risk of dying has been shown to be less than if the patient continued on the waiting list. As more is learned about the expanded donor, pharmacologic interventions and changes in preservation, such as machine perfusion instead of cold storage, may eventually yield results similar to that obtained from ideal donors.

DONOR RESUSCITATION AND STABILIZATION

Clearly, proficient management of the organ donor before retrieval is of paramount importance. However, what may be equally important is the expeditious removal of organs when a donor's condition is difficult to stabilize. In these instances, the organs should be removed as quickly as possible to avoid the risk of the donor having a cardiac arrest or suffering long periods of hypotension.

The hemodynamic management of the donor is of primary importance and includes maintaining an adequate blood pressure (>100 mmHg) and urine output (>100 mL/hr). Once the donor has been declared brain dead, large volumes of fluid and plasma expanders may be necessary to resuscitate the donor to achieve adequate blood pressure and urine output. Hemodynamic monitoring with a central venous catheter (CVP), arterial line, and sometimes a pulmonary artery catheter are usually necessary. Care should be exercised to avoid over-hydration which may cause over-distension of the heart as well as congestion of the lungs and liver which may later affect the function of these organs. Because of the hemodynamic instability caused by severe brain injury due to catecholamine hyperactivity which is followed by hypoactivity, volume alone may not stabilize the donor. Vasopressor support, usually with dopamine, is adequate to stabilize the donor. High-dose dopamine in doses up to 15 µg/kg/min has been shown to be well tolerated. Although vasopressors, such as levaterenol and phenylephrine, should be avoided since they have a greater propensity to cause organ ischemia, they may be necessary to maintain an adequate blood pressure. However, attempts should be made to reduce the dosages by volume resuscitation and the use of
dopamine. If these more potent alpha receptor vasopressors are necessary, they should be used with dopamine at renal doses (3-5 µg/kg/min) to mitigate against splanchnic and renal vasoconstriction.

Usually when urine output is low, volume expansion results in increased urine output. However, diuretics, such as furosemide and mannitol which generally should be avoided in organ donors, can be used to increase urine output as long as there is adequate blood pressure and volume expansion (CVP 12). Many times, however, the problem in brain-dead donors is massive urine output caused by the development of diabetes insipidus due to the lack of the antidiuretic hormone, vasopressin. If urine output exceeds 500 mL/hr, a hypotonic diuresis ensues that should be replaced with hypotonic infusions. If polyuria persists despite adequate fluid replacement, vasopressin may be given at a rate of 0.5-2.0 units per hour to slow diuresis to a more manageable level.

Due to the significant hormonal imbalances seen in brain-dead donors, hormonal management may help to stabilize donors. There has been some evidence that administration of intravenous triiodothyronine (T₃) and arginine vasopressin (AVP) may stabilize the brain-dead donor by restoring some of the hormonal imbalances and circulatory instability. Likewise, brain death may cause varying degrees of cortisol depression and steroid replacement therapy with hydrocortisone may be indicated. Additionally, due to the loss of thermoregulatory function with brain death, many organ donors will become hypothermic unless measures are taken to avoid hypothermia and its sequelae. Hypothermia may lead to cardiac arrhythmias, myocardial depression and hypotension leading to poor tissue and organ perfusion. Organ function may also be compromised from decreased oxygen delivery caused by hypothermia. Infusion of warm fluids and external heating devices will help reduce hypothermia and its adverse effects. Another common problem in brain-dead donors is the presence of coagulopathy caused by tissue thromboplastin release. Coagulopathy, although difficult at times to manage, can be treated with administration of packed red blood cells, fresh frozen plasma, and platelets.

Since many OPOs have recently instituted DCD programs, it is important to mention some important differences in donor management. DCD donors are not brain dead due to preservation of brainstem reflexes, but usually have severe neurologic injury from which they will not recover. The decision to withdraw support has been made by the primary physician and family before notification of the OPO. These donors tend to be hemodynamically more stable with fewer vasopressor requirements than brain-dead donors. The withdrawal of support may occur either in the intensive care unit (ICU) setting, where the patient expires and is conveyed to the operating room, or alternatively in the operating room. In either instance, the patient must be pronounced dead by a physician not affiliated with the transplant team. The patients should be fully supported until withdrawal of support is initiated. The administration of vasodilators and anticoagulants at the time of support withdrawal may be given on a case-by-case basis in accordance with IOM guidelines. Likewise, an additional period of 5 minutes must elapse after death is pronounced before initiating organ retrieval. Because of the
presence of brainstem reflexes, the family must be informed that if the patient continues to have spontaneous respirations beyond a certain period of time (usually > 1 hr), the patient will be returned to the ward or ICU to expire without organ retrieval. Although organs can be transplanted with up to 1 hour of warm ischemia with good results, warm ischemic times of greater than 1 hour will likely result in less than optimal organ function.

**COORDINATION OF MULTIORGAN RETRIEVAL**

OPOs serve several vital functions in the organ procurement process including donor referrals, donor family request and consent, and donor management. Additionally, OPOs coordinate the donation process once consent is obtained. Since the majority of organ donations are multiorgan, OPOs must coordinate assessment of each organ system as well as assessing donor history, laboratory values, including ABO type and tissue type, and any noninvasive testing. If an OPO serves one transplant center, coordination is easier since communication is facilitated among the different transplant teams. However, most OPOs serve more than one center and organ placement and team coordination is logistically more challenging. It is not unusual to have several teams present at an organ procurement including teams for the heart, lungs, liver, pancreas, kidneys, and small bowel as well as teams for tissue donation. Communication is extremely important in facilitating organ procurement in such a way that donor hospitals remain committed to organ donation in their communities. Since most of the techniques for organ procurement are fairly standard with minor center variation in techniques, early communication between teams via the OPO will also help to facilitate a smooth recovery. As a general rule, after the donor is brought to the operating room, dissection of the heart and lungs is followed by dissection of the liver and pancreas, small bowel, and kidneys. Removal of organs usually follows the same sequence as the dissection of the specific organs. Alternatively, all intraabdominal organs may be removed en bloc without in situ dissection of the individual organs. This technique is mandatory in organ retrieval from DCDs. Eye, bone, and tissue donation follows removal of all solid organs.

OPOs also serve a vital postrecovery function at donor hospitals by providing feedback on the ultimate placement and transplantation of the organs retrieved. Also, continued community visibility of the OPO and transplant centers through educational programs will help to maintain and increase organ donation so that more patients will ultimately undergo transplantation. Likewise, donor and recipient families, by interfacing with their communities, can have a profound effect on helping to increase awareness and, ultimately, organ donation.

**SURGICAL TECHNIQUES OF ORGAN PROCUREMENT**

Since most organ procurements involve several organ systems, these combined multiorgan procurements will be described. Once the patient is conveyed to the operating room, prepped and draped, a long incision from the suprasternal notch to the pubis is made. The sternum is split and the cardiac team will open the pericardium, inspect the heart and encircle the superior vena cava, suprahepatic vena cava, and the aorta. The pleural spaces will also be opened and the lungs inspected if being considered for transplantation.
Procurement and Short-Term Preservation of Cadaveric Organs

The intraabdominal portion of the organ procurement commences once the heart team has inspected the heart and lungs. It is important to note that as organ procurement has evolved, less dissection has been shown to be advantageous since it reduces vasospasm, warm ischemia, and decreases the length of operation and donor instability. Liver dissection is performed first and usually involves encircling the supracaeliac aorta, dividing the common bile duct, gastroduodenal artery, and encircling the portal vein. If the pancreas is being used by a center other than the liver center, dissection of the entire celiac artery to the aorta may be performed with the left gastric and phrenic arteries being ligated and the splenic artery encircled. However, prior to ligating the left gastric artery, the donor surgeon must be sure the left hepatic artery does not arise from the left gastric artery. This arterial anomaly is seen in 15% of cases and is visualized in the gastrohepatic omentum. Another hepatic arterial anomaly is the presence of a right hepatic artery arising from the superior mesenteric artery (SMA). This occurs in approximately 10% of cases and can be palpated posterior to the portal vein and common bile duct. Both hepatic arterial anomalies are compatible with hepatic and pancreatic procurement in all cases. Several techniques of vascular reconstruction are available and usually require the use of donor iliac artery grafts.

A new technique of liver procurement involves in situ donor liver splitting for two recipients. Although some centers perform ex vivo liver splitting, in situ splitting may be associated with less bleeding and fewer biliary complications after transplantation. However, a major disadvantage of in situ liver splitting is the additional 1-2 hours required to perform the procedure.

Pancreas dissection involves a Kocher maneuver to mobilize the duodenum as well as dissection of the posterior pancreas to the level of the inferior mesenteric vein (IMV) which is ligated. The first portion of the duodenum and the small bowel just distal to the ligament of Treitz are stapled and the mesenteric vessels are ligated. If the intestine is being recovered for transplantation, the SMA and superior mesenteric vein (SMV) are dissected but not ligated. Also, since the liver and intestine are both transplanted in some patients with short bowel syndrome, the liver, pancreas, and intestine are recovered en bloc without dissection. The pancreas is usually transplanted with the liver and intestine in order to keep the donor porta hepatis intact.

Renal dissection should be minimal and limited to identification and division of the distal ureters. Dissection of the renal arteries and veins as well as mobilization of the kidney should be done only after the intraabdominal organs are infused with preservation solution. This minimal dissection technique helps to limit renal artery vasospasm and subsequent delayed graft function.

Once preparation of each organ to be retrieved is complete, the patient is given 20,000-30,000 units of heparin followed by cannulation of the distal aorta with a chest tube for eventual administration of preservation solution. Also, just prior to organ retrieval, some teams will administer an α-adrenergic antagonist, such as phentolamine, to prevent vasospasm and to ensure more uniform flushout of the intraabdominal organs. Likewise, the heart/lung team may administer prostacyclin, also a vasodilator, during the procurement. Once the SVC is occluded, the aorta is
clamped just proximal to the innominate artery, cardioplegic solution infused, and the caval atrial junction at the level of the diaphragm incised. At the same time, infusion of 1-2 liters of University of Wisconsin (UW) solution is begun via the aortic cannula. The portal vein is then incised, cannulated, and infused with 1 liter of UW solution. Once the heart or heart-lung block is removed, the liver and pancreas are removed followed by removal of the kidneys either en bloc or separately according to the retrieval team preference. Figure 1 depicts the appearance of the liver, pancreas, and kidneys after dissection as well as placement of aortic and portal vein cannulas just prior to removal. After removal, the liver and pancreas are flushed with an additional 200-300 cc UW solution via the SMA, celiac artery, and portal vein and stored in sterile plastic bags on ice at 4°C. If the liver and pancreas are being used at different centers, they are separated and stored separately prior to transport.

The kidneys, if removed en bloc, are usually separated by dividing the vena cava and aorta longitudinally. This will allow identification of multiple renal arteries from within the aorta without risk of injury. If the kidneys are to be

machine perfused instead of cold stored, they may be cannulated en bloc if multiple renal arteries are present or individually if single arteries are present bilaterally. En bloc perfusion requires ligating all lumbar arteries, suturing the proximal aorta, and cannulating the distal aorta. Again, the kidneys are flushed with additional UW solution, placed in sterile plastic bags, and placed on ice at 4°C.

An alternative, rapid en bloc technique of organ retrieval may be used with DCD donors or in donors who have become hemodynamically unstable or who have had cardiac arrest (Fig. 2). This technique involves cannulating the femoral artery and vein or the distal aorta and vena cava, clamping the thoracic aorta, and dividing the esophagus, sigmoid colon, and ureters. While flushing the femoral artery or aorta with UW solution, all intraabdominal organs are removed en bloc by dissecting retroperitoneally starting at the level of the diaphragm and ending at the distal aorta and vena cava which are divided. The portal vein is flushed via the superior mesenteric vein on the back table (inset Fig. 2), and the aorta is incised and each orifice flushed with additional UW solution. If the liver and intestine are to be used for transplant, the aorta should not be divided since it may
be used as a conduit with both the celiac and SMA attached. The organs may be separated at the donor hospital, or alternatively, stored in plastic bags at 4°C and separated upon return to the transplant center.

SAFE TRANSPORT OF ORGANS
Since organs may be transported from one center to another, uniform packaging and storage is essential to ensure all organs are able to be transplanted upon reaching their destination. All organs must be placed in triple sterile plastic bags as well as a rigid container and placed on ice in a 1-1/2" thick polystyrene container. All containers must be labeled, donor paperwork included, and an additional red top tube of blood sent to the receiving center. Depending on the organ and distance to be traveled, transportation may be by ground, commercial flight, or chartered jet. If the organs retrieved are not being sent to other centers, they may be safely stored in triple sterile bags on ice in insulated coolers. The outer container must be moisture resistant and clearly marked with a UNOS donor identification number and a biologic hazard designation label.

SHORT-TERM ORGAN PRESERVATION
INJURY DURING PRESERVATION
Preservation of organs after retrieval is clearly one of the cornerstones of successful transplantation. Although organs vary in their tolerance to cold ischemia, injury to numerous cellular systems begins to occur immediately upon removal. Hypothermia suppresses, to a degree, these changes, but injury during hypothermia still occurs but at a slower rate. Since hypothermic-induced cell swelling is a major source of injury during preservation, most organ preservation solutions are formulated to prevent swelling at cold temperatures. The addition of impermeants such as gluconate, lactobionate, and saccharides such as raffinose, help prevent hypothermic-induced cellular swelling.

Several other phenomena have also been implicated in cell injury during preservation and have been studied extensively. Numerous cellular functions including maintenance of the cellular cytoskeleton requires energy in the form of adenosine triphosphate (ATP). Loss of energy-generating capabilities due to mitochondrial damage or loss of precursors will lead to irreversible cell injury and death upon reperfusion. This concept forms the basis for adding ATP precursors in the form of adenine, adenosine, and ribose to organ preservation solutions. Oxygen-free radical formation after reperfusion has also been implicated in cellular injury during preservation. Suppression of free-radical formation or the addition of free-radical scavengers such as allopurinol, may be beneficial in preservation solutions. Likewise, breakdown of cellular metabolites, such as glycogen and glutathione, may lead to injury and addition of these metabolites may be important in successful organ preservation. Also, activation of catabolic enzymes such as phospholipases and proteases and activation of the arachidonic cascade will lead to cell injury and methods to block their activation may lead to better organ preservation.
CLINICAL ORGAN PRESERVATION
The goals of organ preservation are to maximize organ utilization and maintain excellent organ function while providing safe transport time as well as time for recipient preparation. Currently, the UW solution is primarily used for preservation of intraabdominal organs. Although this solution is used by some centers for heart and lung preservation, many other solutions are also utilized. The components of the UW solution are shown in Table 5.

RENAL PRESERVATION
Currently, there are two methods of preserving kidneys for transplantation: static cold storage or continuous machine perfusion. The majority of centers use cold storage due to simplicity but experience a higher rate of delayed graft function (DGF) than with machine perfusion. Although previously not thought to be important, early DGF appears to predict long-term graft survival. Also, with more expanded donors being utilized, including DCD donors, continuous machine perfusion may be beneficial in preserving organ function. The machine perfusion solution is similar to UW cold storage solution except that lactobionate is replaced by gluconate. As a general rule, cold-stored kidneys should be implanted within 18-24 hours and machine-perfused kidneys within 24-30 hours of removal.

PANCREAS PRESERVATION
The UW solution has been used safely to preserve the pancreas on average 16 hours. Although attempts have been made to perfuse the pancreas experimentally, it has not been met with much success. Interestingly, the pancreas clinically appears to tolerate periods of cold ischemia better than the liver.

LIVER PRESERVATION
Liver function and success after transplantation is dependent not only on donor and recipient factors, but also on good preservation. Preservation of the liver not only involves preservation of the parenchyma, but also preservation of the biliary epithelium, as well as the vascular endothelium, particularly the

<table>
<thead>
<tr>
<th>Table 5. Components of the University of Wisconsin (UW) Solution</th>
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<tr>
<td>Lactobionate (K)</td>
</tr>
<tr>
<td>KH₂PO₄</td>
</tr>
<tr>
<td>Glutathione</td>
</tr>
<tr>
<td>Adenosine</td>
</tr>
<tr>
<td>MgSO₄</td>
</tr>
<tr>
<td>Allopurinol</td>
</tr>
<tr>
<td>Raffinose</td>
</tr>
<tr>
<td>HES</td>
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</table>

mOsm/L = 320; pH = 7.4
endothelium of the hepatic artery. Prior to the development of UW solution, liver preservation was limited to approximately 6 hours. After the clinical introduction of UW solution, it was believed that extended preservation beyond 12 hours was safe. However, it became apparent that rates of primary nonfunction, biliary complications, and hepatic artery thrombosis increased as preservation time increased. Also, preservation injury may lead to increased rates of rejection via upregulation of MHC class I and II antigens, which in turn may lead to graft loss. Although preservation beyond 12 hours can be achieved, rates of primary nonfunction and initial poor function are increased. For this reason, most transplant centers attempt to limit preservation of the liver to 12 hours or less. In an era of donor shortages, every effort should be made to minimize retransplant rates and this can be achieved by minimizing cold ischemia times. Longer term preservation may only be achieved by machine perfusion which has been shown experimentally to be more successful than cold storage.

HEART AND LUNG PRESERVATION

Although a variety of preservation solutions have been developed for heart and lung preservation, preservation of the intrathoracic organs is still limited to 4-6 hours.

STRATEGIES TO MINIMIZE ISCHEMIC DAMAGE

The use of expanded donors including DCDs where periods of hypotension, hypoxia, and warm ischemia are encountered has provided us with opportunities to examine limits and develop strategies to help minimize damage. Although any period of warm ischemia had previously been thought to be inconsistent with organ donation, most organs will tolerate short periods of warm ischemia. Clinical experience with DCDs indicates that the kidneys, liver, pancreas and the lung will tolerate 30-60 minutes of warm ischemia and will still function adequately after transplantation. Administration of anticoagulation with heparin will help prevent small vessel occlusion and administration of pharmacologic agents, such as phentolamine, will help prevent vasospasm and enhance better flush and preservation of donor organs. Administration of nitric oxide precursors, such as L-arginine and nitroglycerin, either to donors or to preservation solutions has been shown experimentally to mitigate warm ischemic damage. Evidence is mounting supporting continuous machine perfusion of kidneys retrieved from expanded or DCDs. Warm ischemic damage can be limited and perhaps improved during cold preservation by continuously supplying substrates for repair and energy production upon reperfusion. Delayed graft function in machine-perfused kidneys retrieved from DCDs has been shown to be similar to DGF rates in cold-stored kidneys retrieved from ideal donors. Interestingly, brain death itself has been shown to have a detrimental effect on organ function after transplantation. In addition to the marked hormonal imbalances that occur with brain death,
organ injury may occur by activating T lymphocytes and the inflammatory response via cytokine release. This response and subsequent organ injury has been shown experimentally to be abrogated by administration of agents that block T-cell costimulation. Since hypothermia-induced cell injury increases with increasing cold ischemia time, preservation times should be minimized, particularly in expanded donors. Likewise, in clinical transplantation, one of the only factors that can be controlled is preservation time and this should be minimized to prevent wastage of organs.

**CONCLUSION**

Transplantation has become the treatment of choice for patients with end-stage organ failure. Results have improved due to refinements in surgical technique, immunosuppression, preservation, and patient management. Unfortunately, organ donation has not kept pace with the ever-increasing demand for transplantation. Although the techniques described in this chapter on organ procurement and preservation are important, they cannot be applied without the generous gift of organ donation. This is also true for nearly every other advance made in clinical transplantation. Therefore, increasing the number of patients who receive the gift of life through increased organ donation must now be our highest priority.

**SELECTED READINGS**

Liver Transplantation

Michael M. Abecassis, Andres T. Blei, Alan Koffron, Steven Flamm and Jonathan P. Fryer

INTRODUCTION
Orthotopic liver transplantation is the accepted therapeutic option of choice for acute and chronic end-stage liver disease. The indications and contraindications to liver transplantation have become standardized, as has the operative and postoperative management. This chapter will address the evaluation and management of patients with acute and chronic liver failure with particular emphasis on recipient selection, operative and postoperative management, and will consist of a practical approach to patients undergoing liver transplantation. Our goal is to provide helpful guidelines to caregivers involved in the care of these complex patients.

Liver failure can present as either acute (fulminant and subfulminant failure) or chronic (advanced cirrhosis). The term decompensated cirrhosis reflects the presence of one or more complications. Each disease etiology presents unique features and it is therefore important to recognize these distinctions. In the pretransplantation era, liver failure was associated with an almost universal fatal outcome, with a spontaneous survival in fulminant hepatic failure of 10-20% and a 1-year mortality in decompensated cirrhosis of >50%. In contrast, liver transplantation patient survival outcomes are presently >85% at one year and >70% at five years, underlining the application of liver transplantation as the standard of care in patients with both acute and chronic liver failure. In addition, the advent of both split liver transplant and live-donor liver transplantation offers additional hope to patients with liver failure in the presence of an ever-growing cadaveric organ shortage.

A. LIVER TRANSPLANTATION FOR PATIENTS WITH ACUTE LIVER FAILURE
Acute liver failure (ALF) is often used synonymously with fulminant liver failure. ALF is defined as an acute hepatic deterioration not preceded by evidence of chronic liver disease, which has progressed from the onset of jaundice to the development of hepatic encephalopathy in less than 8 weeks.1

Subsequent refinements include a division between fulminant (<2 weeks) and subfulminant hepatic failure (>2 weeks), a difference that reflects the greater predominance of brain edema and intracranial hypertension in patients with a shorter interval between the onset of jaundice and the development of encephalopathy. More recently, a differentiation between hyperacute (<1 week), acute (1-4 wks) and subacute failure (>4 wks) has been suggested. Both drug-induced hepatic failure and an indeterminate etiology appear to be more commonly associated

1Liver and Intestinal Transplantation, edited by Frank P. Stuart, Michael M. Abecassis and Dixon B. Kaufman. ©2004 Landes Bioscience.
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with a longer interval. There are also geographic differences in the etiology of fulminant hepatic failure. Hepatitis E is a common cause of ALF during pregnancy in India but is not seen in the United States. A recent survey of 295 cases in the U.S. (Table 1) showed acetaminophen intoxication as a leading cause, followed by nonA-nonE (also termed cryptogenic) and drug-induced failure.\(^2\) Acetaminophen toxicity was associated with the best spontaneous survival (60%), and it is important to recognize its etiologic role in patients with either underlying alcohol consumption or with poor food intake, in whom lower daily doses (4 grams rather than 10-12 grams) may induce severe liver injury. The cause of nonA-nonE fulminant hepatitis remains elusive. Although a transmissible agent has been implicated, hepatitis C, hepatitis G or TTV (transfusion-transmitted virus) have been shown not to be the culprits. Drug-induced hepatic failure has a particularly poor prognosis and spontaneous survival is rare once encephalopathy develops.

Clinical evidence of intracranial hypertension include, hyperventilation, opisthotonus, hyperpronation-adduction of the arms, cardiac arrhythmia, myoclonus, seizures, poorly reactive pupils.

Patients with ALF present initially with vague symptoms, such as anorexia and malaise. Attention by patients and their caregivers may not focus on the diagnosis of liver failure until jaundice is evident. Patients often describe a syndrome suggestive of and consistent with a viral illness. When jaundice is identified, liver function tests typically reveal massive elevations in AST and ALT, elevated bilirubin, significant elevation in the PT, and, in some patients, metabolic acidosis. If Tylenol overdose is suspected, acetaminophen levels should be obtained and the patient should be started on IV acetyl cysteine (Mucomyst). A delay in diagnosis may lead to referral of a patient with ALF late in the clinical course, resulting in advanced cerebral edema.

Table 1. Etiology of fulminant hepatic failure in the United States\(^2\)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>N</th>
<th>%</th>
<th>Survival (Excludes Death or Transplantation)</th>
</tr>
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<tbody>
<tr>
<td>Acetaminophen</td>
<td>60</td>
<td>20%</td>
<td>60%</td>
</tr>
<tr>
<td>Hepatitis nonA-E</td>
<td>44</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>33</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>30</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>21</td>
<td>7%</td>
<td>35%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>122</td>
<td></td>
<td>Wilson’s disease, acute fatty liver of pregnancy, Budd-Chiari Syndrome mushroom intoxication, ischemic injury, tumor infiltration, autoimmune hepatitis, rare viruses (herpes, adenovirus).</td>
</tr>
</tbody>
</table>

Total of series 295

Fulminant hepatic failure typically affects young individuals who had previously been in a perfect state of health and, prior to the availability of liver transplantation, was associated with 80 to 90 percent mortality, especially in patients who progressed to grade 3 or 4 hepatic encephalopathy. With successful transplantation, > 90% of patients survive.\(^3\) Although many factors contribute to the deterioration and death of these patients, the terminal event is typically brainstem herniation as a result of progressive brain swelling. Hepatic encephalopathy is typically divided into 4 stages. Furthermore, coma in stages 3 and 4 is subdivided into 4 grades (Table 2).
Liver and Intestinal Transplantation

It is essential that these patients be admitted and monitored closely in a specialized liver unit where frequent surveillance of their LFTs, PT, CBC, blood gases, blood sugars, electrolytes, and neurological status is performed. With Tylenol overdose, liver transplantation can be prevented if therapy is initiated early. With progression of encephalopathy to stage 3 or 4, the patient should be intubated for airway protection, as these patients have a very high incidence of aspiration as they deteriorate neurologically. An NG tube should be placed at this time and lactulose initiated. The patient should be started on an H2-blocker to prevent ulceration. A Foley catheter should be placed, as well as an arterial line. Central venous monitoring should be entertained if there is a deterioration in renal function or hemodynamic instability. An intracranial pressure monitor should be placed if the patient’s neurologic status cannot be followed clinically, in order to accurately assess progressive brain swelling. Cerebral perfusion pressures determined by subtracting the intracranial pressure from the mean arterial pressure provides a marker for cerebral perfusion. In the case of sustained untreatable cerebral hypoperfusion, the patient may no longer be considered a transplant candidate since irreversible brain injury may occur. If there is evidence of ongoing brain swelling, hyperventilation and/or mannitol may help temporarily.

Prior to the availability of liver transplantation, many non-surgical approaches were attempted in patients with acute liver failure including exchange transfusions, steroids, hemodialysis, and charcoal hemoperfusion. Unfortunately, none of these approaches have been particularly successful. There is new evidence that hypothermia may help to delay brain swelling which is often the terminal complication, but further assessment of this approach is needed. Presently, liver transplantation is considered the best therapeutic option for acute liver failure not thought to be reversible. The criteria for determining whether a patient will need liver transplant or not include factor V level less than 30%, pH less than 7.3%, INR > 6.5, stage 3 or 4 encephalopathy, and lack of response to medical therapy within 20 to 48 hours (Table 3).

<table>
<thead>
<tr>
<th>Table 2a. Hepatic encephalopathy</th>
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<tbody>
<tr>
<td>Stage 1</td>
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<tr>
<td>Stage 2</td>
</tr>
<tr>
<td>Stage 3</td>
</tr>
<tr>
<td>Stage 4</td>
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</table>

<table>
<thead>
<tr>
<th>Table 2b. Grading of coma in stages 3 and 4</th>
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<tbody>
<tr>
<td>Grade 1</td>
</tr>
<tr>
<td>Grade 2</td>
</tr>
<tr>
<td>Grade 3</td>
</tr>
<tr>
<td>Grade 4</td>
</tr>
</tbody>
</table>

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Early referral to a liver transplantation center is essential since: (a) it is difficult to predict which patients will recover spontaneously; (b) deterioration can occur very suddenly; (c) there is a shortage of donor organs and the chance of receiving a transplant is greater with early placement on the waiting list; and (d) once brainstem herniation has occurred, patients are not salvageable by liver transplant or by any other means.

It is important to recognize etiologies of fulminant hepatic failure in which transplantation is contraindicated. These include diffuse infiltration of the liver by lymphoma or extensive liver metastases as an initial manifestation of malignancy. Hepatic ischemia can be a manifestation of left-sided ventricular failure without signs of congestive heart failure. Acute hepatic vein thrombosis, with fulminant failure as a result of venous outflow block, is best treated with a decompression procedure (side-to-side portacaval shunt) rather than organ replacement.

**Options for Hepatic Support**

Due to the severe shortage of human donors, many patients with acute liver failure die waiting for a suitable organ. For this reason, these patients should be referred to centers which are not only capable of liver transplantation, but which are also capable of supporting such patients until an organ becomes available. In addition to standard medical supportive measures, several strategies are being developed to provide temporary hepatic support (Table 4). These options are discussed in the ensuing section.

Charcoal hemoperfusion systems have been evaluated as artificial liver support devices. Although some studies have suggested a survival advantage with fulminant hepatic failure of certain etiologies, most patients do not appear to benefit. Other forms of artificial liver support have included dialysis-like systems coupled

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**Table 3. Criteria for transplantation of acute liver failure**

**Kings College Criteria**

- Acetaminophen toxicity
  - ph < 7.30 (after hydration and regardless of degree of encephalopathy)  
  - or  
  - INR > 6.5  
  - creatinine > 3mg/dl  
  - Encephalopathy III-IV
- Non-acetaminophen etiology
  - INR > 6.5 irrespective of degree of encephalopathy
  - or 3 of the following five criteria
  - Age < 10, > 40
  - Etiology: nonA-E hepatitis, drugs
  - Duration of jaundice before encephalopathy > 7 days
  - INR > 3.5
  - Serum bilirubin > 17.5 mg%.

**Clichy Criteria**

- Factor V < 20% (age < 30 years) or 30% (age > 30 years)
- Confusion and/or coma
Liver and Intestinal Transplantation

One system in this category, which is currently undergoing clinical trials, utilizes dialysis fluid containing charcoal and a cation exchange resin to bind toxic substances in the blood. A pilot study performed in acute liver failure patients showed that this system was well tolerated and could produce biochemical improvements, although its ability to reverse the progression to terminal brain swelling has not been demonstrated. A second support device, the molecular absorbents recirculating system (MARS), consists of a dialysis system where the polysulphone membrane is impregnated with albumin and the dialysate enriched with albumin to facilitate the removal of toxic metabolites. A third artificial liver support system, the microsphere based detoxification system (MBS), involves plasma recirculation at very high flow rates with all flow being exposed to particle size absorbents, which provide a large surface area for absorption.

Bioartificial Liver Support Systems

Another approach consists of a Bioartificial Liver (BAL). In this system, plasma obtained with a centrifugal plasma separator is subsequently perfused through microcarrier bound porcine hepatocytes. This device has been studied clinically with some promising early results. It is difficult to determine what role the hepatocytes played in these instances since a charcoal column is also included in the circuit. An alternative approach, the Extracorporeal Liver Assist Device (ELAD), utilizes blood perfusion through hollow fiber membranes surrounded by cells of a human tumor cell line (C3A).

Hepatocyte Transplantation

More recently, hepatocyte transplantation has been used successfully to treat certain metabolic disorders and preliminary data indicate that it may also be effective in acute liver failure. However, the number of cryopreserved hepatocytes required to achieve success may limit the utility of this approach.

Extracorporeal Liver Perfusion

This approach overcomes many of the problems associated with the previous approaches including: (a) the inability to support all the functions provided by the liver and (b) inability to provide enough hepatic support to overcome the derangement associated with fulminant hepatic failure. Both human and porcine livers have been used successfully with this approach. Since the shortage of human

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**Table 4. Options for hepatic support**

<table>
<thead>
<tr>
<th>Artificial liver support devices</th>
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<tbody>
<tr>
<td>Bioartificial livers</td>
</tr>
<tr>
<td>Hepatocyte transplantation</td>
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<tr>
<td>Extracorporeal liver perfusion</td>
</tr>
<tr>
<td>Artificial liver support systems</td>
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</table>
livers remains the essential problem in patients with fulminant hepatic failure, the only human livers which will be available for this technique will be those of poor quality and that are not usable for transplantation.

With this approach, an extracorporeal circuit perfuses blood from the femoral vein, incorporates a centrifugal pump and a tissue oxygenator which lead to the porcine liver (which is kept in a sterile temperature controlled environment at the bedside), and then returns the blood to the patient through the jugular or axillary vein (Fig. 1). This approach has been successful in the past in providing both biochemical and neurological improvement in patients. More recently, successful ‘bridging’ to successful liver transplantation has been achieved. The limiting factor with porcine livers has been a vascular rejection that occurs within 2 to 4 hours of perfusion due to preformed human antibodies to porcine endothelium.

Because of severe organ shortages, recent interest in xenotransplantation has led to strategies which have overcome the early rejection associated with pig to primate transplantation. The most exciting of these approaches has been the development of pigs which are transgenic for human complement regulatory proteins (CD55 and CD59). In this setting, complement activation does not occur in pig endothelium and early rejection can be potentially avoided. Transplantation of organs from transgenic pigs to non-human primates extends kidney graft survivals from hours to weeks when compared to organs from non-transgenic pigs. Therefore, it is anticipated that prolongation of survival will provide a period of hepatic support, which will clearly exceed that experienced with non-transgenic pig livers.

Fig. 1. Extracorporeal liver perfusion circuit (see text).
B. LIVER TRANSPLANTATION FOR PATIENTS WITH CHRONIC LIVER DISEASE

Complications of Cirrhosis
Cirrhosis can arise from two major categories of disease: hepatocellular and cholestatic. Within both groups, further subclassifications can be delineated (Table 5). While all etiologies share common features of liver failure once an advanced stage is reached, unique aspects of each etiology influence management during and following transplantation.

Liver transplantation is also indicated for patients with certain metabolic diseases that can present with liver failure in the absence of cirrhosis (Table 6). This is more common in the pediatric population, but can occasionally extend into young adulthood. Other congenital abnormalities (urea cycle enzyme deficiencies, familial hypercholesterolemia, familial amyloidosis) can present with extrahepatic manifestations that are so severe that liver transplantation is recommended in the absence of hepatic disease. Finally, a miscellaneous group of chronic disorders may require transplantation in the absence of both cirrhosis and hepatic failure.

Pathophysiology of Chronic Liver Disease
The pathophysiology of advanced liver disease results in two cardinal pathophysiological abnormalities: hepatocellular failure and portal hypertension. In acute liver failure, portal hypertension is seldom a clinical problem while in cirrhosis, an increased portal pressure may give rise to complications while hepatocellular function is preserved. The importance of these two factors is recognized in the Child-Turcotte-Pugh classification, a prognostic tool in patients with cirrhosis (Table 7).

Portal Hypertension
Portal pressure rises as a result of both a high hepatic vascular resistance and an increased portal venous inflow. The anatomical site of the increased vascular resistance in the liver will vary with different etiologies of cirrhosis, the hepatic sinusoids being the critical site for alcoholic cirrhosis. A functional component to this resistance may also be present, as transformed stellate cells in the sinusoids may respond to vasoconstrictive stimuli, such as endothelin. Once a critical level of portal hypertension is reached (hepatic venous pressure gradient of 10-12 mmHg, defined by the pressure gradient between the portal vein and the hepatic vein), portal-systemic collaterals form in an attempt to decompress the portal system. Portal hypertension is sustained by the development of increased portal venous inflow.

This increase in portal flow is part of a generalized hemodynamic abnormality of both acute and chronic liver failure consisting of a hyperdynamic circulation. The mechanisms which contribute to the arteriolar vasodilatation are under investigation, but an increased production of nitric oxide in the vascular endothelium and hence low systemic vascular resistance may explain the levels of circulating cytokines (such as TNFα) that are present in patients with both acute and chronic liver disease. The hyperdynamic state has repercussions on other organs, such as lung and kidneys, which pose specific problems in the management of the patient before, during and after liver transplantation (Fig. 2).
Liver Transplantation

Hepatocellular Failure

The "intact hepatocyte" theory of hepatocellular failure postulates that a critical number of viable hepatocytes is needed to maintain liver function. The "sick hepatocyte" theory suggests a generalized malfunction of individual cells. There may be elements of both theories in advanced cirrhosis. On a practical level, the 3 biochemical tests used in the Child-Turcotte-Pugh classification have not been superseded by more sophisticated tests, such as those that arise from tests of drug metabolism (e.g., lidocaine, caffeine).

Table 5. Cirrhosis and liver transplantation

<table>
<thead>
<tr>
<th>Hepatocellular Diseases</th>
<th>Special Considerations for Liver Transplantation (OLT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis</td>
<td>Virus should be non-replicating (HBV-DNA negative)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Co- or superinfects Hepatitis B. Rare in the US</td>
</tr>
<tr>
<td>Hepatitis D</td>
<td>Important to exclude alcohol as comorbid factor</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Pre-OLT medication may affect post-OLT bone disease</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Examples: nitrofurantoin, alphamethylpypodopa</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Drug-induced</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>Abstinence and social support critical for OLT.</td>
</tr>
<tr>
<td></td>
<td>Increasing prevalence of cirrhosis. Rate of recurrence.</td>
</tr>
<tr>
<td></td>
<td>Example: Amiodarone.</td>
</tr>
<tr>
<td>Chronic Budd-Chiari syndrome</td>
<td>R/O myeloproliferative syndrome, thrombotic tendency.</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>Cardiac involvement results in increased OLT morbidity.</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Lung disease is rare in the presence of liver cirrhosis deficiency</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin</td>
<td>Wilson's disease</td>
</tr>
<tr>
<td>Glycogen storage</td>
<td>OLT for acute disease not amenable to medical therapy</td>
</tr>
<tr>
<td>disease type I/III</td>
<td>Can present in early adulthood.</td>
</tr>
</tbody>
</table>

Cholestatic Diseases

<table>
<thead>
<tr>
<th>Disease of intrahepatic bile ducts</th>
<th>Kasai procedure may offer relief for a few years before OLT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary atresia</td>
<td>Bone disease can be especially problematic post-OLT.</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Examples: Chlorpromazine, tolbutamide.</td>
</tr>
<tr>
<td>Drug-induced disease</td>
<td>Byler's syndrome, arteriohepatic dysplasia. Inisipissated bile syndrome leading to cirrhosis.</td>
</tr>
<tr>
<td>Familial cholestasis</td>
<td>Drug-induced</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Drug-induced</td>
</tr>
</tbody>
</table>

Disease of extrahepatic bile ducts | Secondary cholangiocarcinoma may contraindicate OLT. |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary sclerosing</td>
<td>Requires Roux-en-Y anastomosis at OLT.</td>
</tr>
<tr>
<td>cholangitis</td>
<td></td>
</tr>
<tr>
<td>Secondary biliary cirrhosis</td>
<td></td>
</tr>
</tbody>
</table>
Recipient Evaluation

A thorough evaluation of the subject’s candidacy for liver transplantation must include an assessment of the need, urgency and technical feasibility of OLT. The acuity and extent of the investigation is frequently determined by the severity of liver disease. In patients with fulminant hepatic failure, in whom therapeutic decisions need to be made over a short interval, the evaluation phase may need to be streamlined and accelerated. The recipient evaluation includes the investigation of four major areas:

i) Assessment of Etiology of Liver Disease

This aspect requires an adequate history, physical examination and laboratory testing (Table 8). Radiologic imaging of the liver and endoscopic evaluation of the GI tract are also needed. A liver biopsy, obtained either percutaneously or via the transjugular route in patients with ascites and severe coagulopathy, can provide a definitive diagnosis and may be critical in selected patients with acute liver failure and for others in whom alcoholic hepatitis is suspected.
ii) Assessment of the Complications of Cirrhosis

Several complications of cirrhosis signal the need to proceed with liver transplantation and require selective diagnostic tests. The tools to complete such work-up are delineated in Table 9.

iii) Assessment of Exclusion Criteria (Contraindications)

Older recipients are increasingly referred for evaluation. Although there is no absolute chronological limit for age above which transplantation is contraindicated, evaluation of physiological age requires a thorough clinical assessment. Adequate evaluation of cardiac function is critical. Obese and diabetic individuals
Liver and Intestinal Transplantation

are also at risk of atherosclerotic vascular disease and require full cardiovascular evaluation. While non-invasive cardiac testing may be adequate in the younger, otherwise healthy candidate, this will be insufficient for patients at risk (Table 10). Other organs also require attention. Bone disease post-transplantation is affected by the pre-transplantation bone status (especially in older patients, those receiving corticosteroids pre-transplantation and those with cholestatic liver disease) and post-transplant medications. Bone densitometry is required in such individuals for adequate evaluation and follow-up.

Pulmonary Function Tests
Co-existing medical conditions need to be ascertained. Uncontrolled infection outside the biliary tree is an absolute contraindication to transplantation. In the case of malignancy, metastatic hepatobiliary and extrahepatic malignancy are also absolute contraindications. For other neoplasias, a waiting period of 5 years after treatment of a solid organ tumor and 2 years for a hematological disorder is recommended. The presence of AIDS is a contraindication to transplantation, as

Table 8. Testing to assess etiology of liver disease (blood tests)

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B, HBV-DNA, HBeAg, anti-HBe, and anti-Delta Abs.</td>
</tr>
<tr>
<td>Hepatitis C, HCV-RNA, HCV genotype</td>
</tr>
<tr>
<td>Autoimmune: Anti-smooth muscle Ab (ASMA), Antinuclear Ab (ANA), Antimitochondrial Ab (AMA).</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin level/phenotype.</td>
</tr>
<tr>
<td>Wilson: Ceruloplasmin, 24 hr urine copper, liver copper.</td>
</tr>
<tr>
<td>Hemochromatosis: Iron saturation, ferritin, HFE gene test.</td>
</tr>
<tr>
<td>Blood group (for listing purposes)</td>
</tr>
</tbody>
</table>

Table 9. Testing to assess the complications of liver disease

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood gases: t/o hypoxemia/hepatopulmonary syndrome</td>
</tr>
<tr>
<td>Liver imaging: t/o hepatocellular carcinoma (HCC)</td>
</tr>
<tr>
<td>Serum alpha-fetoprotein, CA19-9: t/o HCC, cholangiocarcinoma</td>
</tr>
<tr>
<td>Doppler ultrasound: t/o portal vein thrombosis (PVT)</td>
</tr>
<tr>
<td>Upper gastrointestinal endoscopy: Assess portal hypertension</td>
</tr>
<tr>
<td>Bone densitometry: Selected patients</td>
</tr>
<tr>
<td>Neuropsychological testing: Selected patients</td>
</tr>
</tbody>
</table>

Table 10. Testing to exclude contraindications

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious disorders: HIV, syphilis, CMV, EBV, toxoplasmosis</td>
</tr>
<tr>
<td>Malignancy: Colonoscopy in primary sclerosing cholangitis (ulcerative colitis)</td>
</tr>
<tr>
<td>ERCP in primary sclerosing cholangitis (cholangiocarcinoma)</td>
</tr>
<tr>
<td>In HCC: bone scan, lung CT (metastatic workup)</td>
</tr>
<tr>
<td>Screening (colon, breast, cervical, prostate cancer)</td>
</tr>
<tr>
<td>Cardiopulmonary status: CXR, ERG, 2D-Echo (routine)</td>
</tr>
<tr>
<td>Thallium stress test, coronary angiography (patients at risk)</td>
</tr>
</tbody>
</table>
post-transplant immunosuppression accelerates the course of the disease. Irreversible brain damage and multiorgan failure also preclude the liver transplant procedure.

**iv) Psychosocial Assessment**

It is important to predict the ability of the candidate to exhibit discipline and responsibility during his post-transplant care. Assessment of the patient’s lifestyle, psychological stability (including his/her perception of disability) and extent of family support require interaction with Psychiatry/Social Work support services. This evaluation is critical for patients with alcoholic liver disease, in whom the ability to abstain from alcohol post-transplant can be assessed by the ability to abstain before transplantation (at least 6 months), employment history and a support structure (family, friends). Patterns of drug abuse need to be explicitly discussed. Emergency psychiatric assessment is needed for acute hepatic failure from ingestion of acetaminophen with suicidal intent, as an interview should occur before the patient develops an altered mental state. If the latter is present, the team needs to rely on the individual history (e.g., previous suicidal attempts) and a family interview to reach a decision.

**SELECTION CRITERIA AND LISTING PROCESS**

The decision to proceed with transplantation requires a careful assessment of the etiology and staging of liver disease, the complications of cirrhosis, potential contraindications, and a comprehensive psychosocial evaluation. The results of the work-up may not be clear-cut and a determination to exclude a candidate can be difficult, especially when the alternative outcome to the patient is certain death. A Multidisciplinary Transplant Review Board, composed of all individuals involved in the different aspects of care of the transplant recipient, needs to weigh dispassionately the pros and cons of each candidate in order to reach a rational decision. Input from consulting physicians, psychiatry, ethicists and social workers is critical to resolve specific situations. Each candidate must have an advocate who presents his/her case to the selection committee and the vote to proceed must be unanimous.

The patient needs to meet minimal listing criteria before placed in the waiting list (Child-Turcotte-Pugh score of at least 7 for most causes of cirrhosis). Once listing is approved, the patient is awarded a priority based on the current UNOS organ allocation scheme, the Model for End Stage Liver Disease (MELD). This scheme, based on predicted three-month mortality of patients awaiting liver transplant, uses laboratory values to generate a score which determines priority. The MELD equation incorporates serum creatinine, serum bilirubin, and international normalized ration (INR) as illustrated in Table 11.

### Table 11. Model for end stage liver disease (MELD)

<table>
<thead>
<tr>
<th>MELD Score</th>
<th>=0.957 x Log (creatinine mg/dl) + 0.378 x Log (bilirubin mg/dl) + 1.120 x Log (INR) + 0.643</th>
</tr>
</thead>
</table>
CLINICAL MANAGEMENT WHILE AWAITING LIVER TRANSPLANTATION

With the increasing waiting times, maintaining the patient in an acceptable medical condition in order to undergo a successful liver transplant is a challenge for the managing team. Both prophylactic measures and therapeutic interventions are needed to deal with the numerous complications that can arise.

TIMING OF LIVER TRANSPLANTATION

A sound knowledge of the natural history of disease is essential in the decision making process vis-à-vis the timing of transplantation. The development of complications typically results in an upgrade of the priority status for transplantation in exchange for a higher surgical mortality and a large increase in cost. This apparent paradox cannot be resolved given the current organ shortage. In acute liver failure, prognostic criteria have been developed to assess the necessity for urgent liver transplantation. In patients with chronic liver disease, the prevention and management of potential complications requires an inordinate amount of attention and comprehensive care on the part of the clinician.

PROPHYLAXIS OF COMPLICATIONS

Patients in the waiting list are at risk for developing HCC. Screening with ultrasound and alpha-fetoprotein level determination every 6 months is performed by most transplant centers. Screening upper endoscopy to rule out the presence of medium/large varices with red wheals is also recommended, as these patients may benefit from prophylaxis of variceal hemorrhage with beta-blockers. Hepatitis B vaccination is seldom useful in advanced stages of liver disease, but is recommended by some centers. Hepatitis A vaccination has become recently available and its utility in patients with liver disease is currently being evaluated.

THERAPY OF COMPLICATIONS

The rationale for each therapy is beyond the scope of this handbook and the reader is referred to standard references. Each of the four major complications has a management protocol (Table 12). However, the development of one complication can trigger additional problems. GI hemorrhage and infection have the potential of aggravating liver and renal function, while intractable ascites impairs respiratory function and aggravates malnutrition. Overt hepatic encephalopathy can result in aspiration pneumonia and may require prophylactic tracheal intubation. Fluid overload in the setting of renal failure and severe hypoalbuminemia requires extracorporeal measures for correction, such as CVVH (continuous venovenous hemofiltration). These patients require extensive and intensive support to overcome these problems.

RECIPIENT OPERATION

When a suitable donor is identified for a recipient, a rapid evaluation of the recipient is done so that any potential contraindications that may have arisen during the waiting period are noted and appropriately investigated. Please refer to the appropriate chapters for donor and anesthetic issues. The ensuing section will address the technical aspects of liver transplantation.
### Table 12. Treatment of complications of cirrhosis

**A. Variceal Hemorrhage**

**Initial hemostasis**
- Pharmacological therapy
  - Vasopressin (0.1-0.4 U/min) and nitroglycerin (start with 1 mg/kg/min iv).
  - Octreotide [100 ucg bolus, 50 ucg/hr infusion (still unproven when given alone)]
- Endoscopic therapy
  - Variceal band ligation preferred over endoscopic sclerotherapy.
  - Fundic varices not amenable to endoscopic therapy in the US.
- Mechanical tamponade
  - Sengstaken-Blakemore tube requires knowledge of potential complications.

**Prevention of early rebleeding**
- Octreotide infusion for 5 days
- Treatment of bacterial translocation: Norfloxacin 400 mg/day.

**Maintenance therapy**
- Pharmacological therapy
  - Propranolol, to reduce portal pressure by 20%, start with 20 mg bid (requires hepatic vein catheterization) or
  - Maximal dosage that reduces heart rate to 25% of baseline or not < 55 beats/minute.
  - If portal pressure reduction not attained, add isosorbide mononitrate 5 mg bid.
- Endoscopic therapy
  - Continue variceal band ligation until eradication of varices (achieved with 4-5 sessions in 40-50% of patients).

**Failure of therapy**
- Shunt surgery, especially distal splenorenal shunt
  - For patients with good liver function (Child 5-7 and no ascites).
- Transjugular intrahepatic portal-systemic shunt (TIPS)
  - Rescue therapy, for patients with poor liver function

**B. Hepatic Encephalopathy**

1. **Correct precipitating event**
   - Cleansing enemas for GI bleeding
   - Volume expansion/electrolyte correction
   - Treatment of infection, (without aminoglycosides!)
   - Antagonism of sedatives (flumazenil, Narcan)

2. **Diet**
   - Protein intake should be at least 0.75-1 g/kg (counteract catabolic state).
3. **Non-absorbable disaccharides**
   - Lactulose po 20-30 cc q 8-12 hours (via NG in ICU)
4. **Zinc sulfate, 300 mg q 12 hours (to increase urea synthesis in liver)**
5. **Antibiotics on intestinal flora**
   - Neomycin (3-6 g/day) for short periods (to avoid toxicity)
   - Metronidazole, start at 250 mg bid.
6. **In stage III-IV encephalopathy, Endotracheal intubation to prevent aspiration**

**C. Ascites**

1. **Diet and fluid balance**
   - Bed rest and low sodium diet (2-4 g/d)
   - Fluid restriction (1L/day) for serum sodium < 130 mEq/l
   - Daily weight, urinary output and fluid balance
2. **Diuretics**
   - With no response to a low sodium diet and a low U_{Na} (r/o dietary non-compliance)
   - Spironolactone (100-400 mg/d) alone or with furosemide (20-160 mg/day)
   - Restrict weight loss to not > 1kg/d when no peripheral edema
   - Careful with diuretic complications
   - Renal impairment
   - Hepatic encephalopathy
   - Hyperkalemia with renal failure (Spironolactone)
STANDARD SURGICAL TECHNIQUE

The recipient operation consists of hepatectomy of the native liver followed by implantation of the donor liver. The native hepatectomy can be difficult, especially in patients with previous upper abdominal operations and severe portal hypertension. The ligamentous attachments of the liver are systematically taken down followed by skeletonization of the hilar structures, namely the bile duct, hepatic artery, and portal vein, in preparation for implantation of the new liver. The retroperitoneal (bare) area is taken down last since most of the blood loss can result from this dissection. Finally, the inferior vena cava (IVC) is encircled below the liver having divided the adrenal vein, and above the liver allowing enough room between the diaphragm and the origin of the hepatic veins for a vascular clamp to be comfortably placed. At this ‘point of no return’, the bile duct is ligated and divided, as is the hepatic artery. Vascular clamps are then placed on the portal vein and the IVC below and above the liver and the liver is removed by transecting the portal vein and the IVC and removing the retrohepatic IVC with the liver.

At this point, hemostasis is achieved as well as possible. Occasionally, the bare area may require coagulation with the argon beam coagulator and a few hemostatic sutures. Depending on the degree of coagulopathy the new liver may need to be implanted while there is ongoing bleeding from the bare area. The donor liver is prepared for implantation on the back table by removing its diaphragmatic attachments including ligation of phrenic veins, removing the adrenal gland and ligation of the adrenal vein, and preparing the arterial and portal venous structures. The donor liver is then brought onto the operative field and end-to-end anastomoses are constructed using running non-absorbable monofilament
suture between donor and recipient suprahepatic IVC first, then the infrahepatic IVC. Prior to completion of the infrahepatic IVC anastomosis, the liver is flushed with 500 cc of cold Ringer’s lactate solution until the effluent from the infrahepatic IVC is clear and, at this point, the IVC anastomosis is completed. Next the portal vein anastomosis is performed end-to-end with running non-absorbable monofilament suture leaving a ‘growth factor’ in order to prevent a narrowing of the anastomosis. In the case of a thrombosed or inadequate portal vein, a donor iliac vein conduit is anastomosed preferably to the confluence of the splenic and superior mesenteric veins (SMV) or alternatively to any patent branch of the portal venous system including the SMV. SMV-to-portal vein grafts are tunneled through the transverse mesocolon. Once the portal vein anastomosis is completed, the clamps are removed in sequence and the liver is thus perfused with portal venous inflow.

Venous-venous bypass (VVP) is occasionally used, prior to completion of the hepatectomy, in order to decompress the splanchnic venous system as well as venous return from the lower extremities. Some centers use VVP routinely, whereas in other centers it is not used at all.18 Most centers use VVP in selected patients, especially when the hepatectomy has been difficult and bloody, or when significant portal hypertensive bleeding is evident especially from the bare area. VVP requires cannulation of both a lower extremity vein, typically the saphenofemoral vein, and an upper extremity or neck vein. This can be achieved either via cut-down or by a percutaneous approach. Partial VVP can also be used, consisting of lower extremity to upper extremity bypass alone, as compared to full VVP which includes a portal venous line in order to decompress the portal vein. The decision to use or not to use VVP may depend on the hemodynamic stability of the recipient upon clamping, especially of the IVC. Rapid infusion can be used to offset some degree of hemodynamic instability during the clamping phase, but if the patient does not tolerate clamping without significant hemodynamic instability, then VVP should be considered (Table 13).

Upon reperfusion of the liver with portal venous inflow, patients can develop a “reperfusion syndrome” consisting of right-sided ventricular failure associated with high filling pressures and systemic hypotension, significant arrhythmias can also occur. This syndrome is usually transient in nature and thought to be secondary to infusion of potassium or acid load from the preserved liver, and from splanchnic and lower extremity venous congestion. Expert anesthetic management and correction of electrolyte abnormalities are needed during this transient period.

<table>
<thead>
<tr>
<th>Table 13. Potential indications for venous-venous bypass</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Severe retroperitoneal collateralization</td>
</tr>
<tr>
<td>2. Poor preoperative renal function</td>
</tr>
<tr>
<td>3. Hypotension following test clamping of the vena cava despite adequate volume loading</td>
</tr>
<tr>
<td>4. Intestinal or mesenteric edema</td>
</tr>
<tr>
<td>5. Fulminant hepatic failure</td>
</tr>
<tr>
<td>6. Inexperience with the procedure</td>
</tr>
</tbody>
</table>
Liver and Intestinal Transplantation

For more details on anesthetic considerations of liver transplantation including monitoring of coagulation please refer to Chapter 8.

The hepatic artery anastomosis is typically performed between the recipient hepatic artery, at the junction of the gastroduodenal artery, and the donor celiac axis using a Carrel patch. Approximately 15 to 20 percent of the time, abnormal arterial anatomy is identified in the donor liver consisting of either an aberrant left hepatic artery emanating from the left gastric artery of the donor, which does not require any particular reconstruction, or an aberrant right hepatic artery originating from the superior mesenteric artery. This latter type of arterial anatomy requires arterial reconstruction on the back bench which most commonly consists of implanting the origin of the aberrant vessel onto the donor splenic artery so that the celiac axis can be used as a single inflow. Occasionally, the inflow from the recipient hepatic artery is inadequate either because of inadequate flow or as a result of abnormal arterial anatomy in the recipient. Donor iliac arteries are routinely harvested as part of the donor procedure and these can be used to construct a conduit between the recipient infrarenal aorta and the donor hepatic artery or celiac axis. This conduit can also be made to originate from the supracleiac aorta, although infrarenal reconstruction is more commonly used. The conduit can be brought to the hilum by creating a tunnel behind the pancreas, but can also be placed anteriorly through the transverse mesocolon.

Once the liver is arterialized and the hepatic artery demonstrates satisfactory flow, hemostasis is achieved, and the bile duct reconstruction is performed using end-to-end choledochocholedochostomy over a T-tube stent. Several variations

Fig. 3. Standard technique. This figure illustrates a completed liver transplantation with vascular and biliary anastomoses.
of this anastomosis have been used. Recently the necessity for a T-tube has been questioned and some centers have elected not to use T-tubes primarily because of an unavoidable rate of biliary leaks following removal of the T-tube, as well as other technical problems associated with the T-tubes. Therefore, an end-to-end choledochocholedochostomy is performed using absorbable interrupted monofilament suture without stenting (Fig. 3). If the recipient bile duct is not appropriate for end-to-end reconstruction, a Roux-en-Y choledochojejunostomy is performed in standard fashion with or without internal stenting (Table 14).

ALTERNATIVE TECHNIQUES

“PIGGYBACK PROCEDURE”
The recipient hepatectomy can be altered to leave the recipient retrohepatic IVC in situ. Thus, during the hepatectomy, the caudate venous branches are ligated and divided individually as the IVC is separated from the liver. Occasionally accessory hepatic veins are encountered particularly to the right lobe and eventually the liver remains attached to the IVC only by the hepatic veins. The hepatic veins can then be either clamped and the ostia used for the IVC anastomosis (Fig. 4A), or suture ligated and another site on the recipient IVC used for anastomosis. The donor IVC is then anastomosed to the recipient IVC in a piggyback fashion by performing either an end-to-side or side-to-side IVC-to-IVC anastomosis. Once the IVC anastomosis is completed, the infrahepatic IVC is used as outflow of portal venous blood (instead of cold Ringer’s lactate) in an effort to wash out preservation solution from the liver and following this, the infrahepatic IVC is ligated. The remaining structures are anastomosed in standard fashion (Fig. 4B).

“SPLIT LIVER PROCEDURE”
Recently, the use of split livers has become routine for selected donor livers for most liver recipients. The liver is typically ‘split’ along the falciform ligament separating the left lateral segment (Couinaud segments II and III) from the remaining liver. The main hilar vascular and biliary structures are retained with the right side of the liver. The left lateral segment is typically transplanted into a child and the remaining liver transplanted into an adult. The transplant procedure for a split liver is identical to that for a whole liver with the exception that hemostasis at

<table>
<thead>
<tr>
<th>Table 14. Indications for choledochojejunostomy</th>
</tr>
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<tbody>
<tr>
<td>1. Donor-recipient bile duct size discrepancy</td>
</tr>
<tr>
<td>2. Diseased recipient bile duct</td>
</tr>
<tr>
<td>a) Secondary biliary cirrhosis</td>
</tr>
<tr>
<td>b) Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>c) Choledocholithiasis</td>
</tr>
<tr>
<td>d) Biliary atresia</td>
</tr>
<tr>
<td>3. Presence of biliary duct malignancy</td>
</tr>
<tr>
<td>4. Poor blood supply to recipient bile duct</td>
</tr>
<tr>
<td>5. Inability to pass biliary probe through ampulla</td>
</tr>
</tbody>
</table>
Fig. 4A and B. A) Piggyback technique. This figure illustrates the preparation for the piggyback cavo-cavo plasty. First, the donor suprahepatic IVC is viewed from the back where a vertical slit is made in the middle of the back wall. This is triangulated to match the triangulated hepatic vein opening on the recipient side. Finally, the liver is viewed after all of the anastomoses have been completed showing an end on view. B) Side view of the piggyback procedure. Showing the triangulated cavo-cavo plasty of the donor suprahepatic IVC and the ligated infrahepatic IVC.
the cut surface needs to be secured and a careful check for biliary leaks in the raw surface needs to be carried out. Split liver transplant, when performed on proper recipients using suitable donor organs has survival results comparable to whole livers, but is associated with a higher rate of surgical complications.\textsuperscript{20,21}

**“Auxiliary Procedure”**

In selected recipients with either metabolic diseases or acute liver failure, auxiliary transplants have been performed. A left lobe resection of the native liver is carried out and a donor left lateral segment or left lobe is transplanted orthotopically by anastomosing the donor left hepatic vein to recipient IVC end-to-side and portal vein hepatic artery and bile duct connections constructed in standard fashion. Nuclear studies are used to follow uptake/function by the donor/recipient liver, and in cases where the native liver recovers, the donor liver is either allowed to atrophy following withdrawal of immunosuppression, or is removed. Alternatively, the donor liver is treated like any other transplanted liver and ultimately becomes the predominantly functioning liver. Differential portal venous flow between recipient and donor liver segments may be responsible for preferential function and hypertrophy.

**Immediate Postoperative Care**

There are three major considerations in the immediate postoperative period: (1) liver function, (2) postoperative bleeding, and (3) general considerations.

1. **Liver Function**

One of the most disastrous complications following liver transplantation is primary nonfunction (PNF). PNF needs to be differentiated from graft dysfunction which encompasses a spectrum ranging from mild graft dysfunction, manifested by elevated liver enzymes and poor early synthetic function, to severe dysfunction manifested by prolonged synthetic dysfunction, some degree of hemodynamic instability, and associated multiorgan dysfunction.\textsuperscript{22} This end of the dysfunction spectrum along with PNF require consideration of urgent retransplantation, whereas mild to moderate dysfunction require close observation and supportive therapy. The appearance of the liver following reperfusion, the production of bile intraoperatively, and the hemodynamic status of the recipient provide intraoperative evidence of liver function (Table 15).

<table>
<thead>
<tr>
<th>Table 15. Helpful signs of hepatic function in the intraoperative period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Restoration of hemodynamic stability</td>
</tr>
<tr>
<td>2. Good renal function evidenced by adequate urine output</td>
</tr>
<tr>
<td>3. Stabilization of acid-base status</td>
</tr>
<tr>
<td>4. Normalization of the coagulation system</td>
</tr>
<tr>
<td>5. Normalization of body temperature</td>
</tr>
<tr>
<td>6. Maintenance of proper glucose metabolism</td>
</tr>
<tr>
<td>7. Adequate bile production</td>
</tr>
<tr>
<td>8. Good texture and color of the liver</td>
</tr>
</tbody>
</table>
However, the first 6 to 12 hours (immediate postoperative period) provide more definitive evidence of liver function. The best indicators of early graft function include normalization of Factor V levels, prothrombin time, and transaminases. In addition, clearance of lactic acidosis, awakening from the anesthetized state, and good renal function provide further affirmation of liver function (Table 16).

2. POSTOPERATIVE BLEEDING

Significant coagulopathy can be present following revascularization of the liver and can be attributed to fibrinolysis, heparin-like effect, and platelet and coagulation factor deficiencies. Under normal circumstances, with a functioning graft, coagulopathy is reversed by the time of abdominal closure. However, complete hemostasis may not be fully achieved at time of closure despite the best of efforts, especially if the recipient is hypothermic and if the operation has been long, difficult, and bloody. This scenario has become uncommon, but can nevertheless occur, especially in the setting of a dysfunctional graft. Under these circumstances, it may be preferable to place appropriate drains or even packs, close the abdomen, and return the patient to the intensive care unit. Close attention to ongoing bleeding despite correction of coagulopathy is essential. This can be achieved with a combination of hemodynamic monitoring, serial hematocrit determinations, and overall condition of the patient including urine output and measuring of drainage output. It may also be helpful to perform hematocrit determinations on the drain fluid. If ongoing bleeding, despite correction of coagulopathy and rewarming of the patient, is suspected, especially if hemodynamic instability and oliguria are present, the patient should be returned to the operating room for evacuation of hematoma and identification of ongoing bleeding. At this time, generalized oozing may have improved so that specific bleeding sites can be more easily identified and oversewn, especially in the bare area. The presence of a dry operative field at the time of abdominal closure however should not be viewed as evidence that postoperative bleeding cannot occur. Postoperative bleeding should be considered highly in the differential diagnosis of hypotension and oliguria in the immediate postoperative period even in patients in whom a dry field was achieved intraoperatively.

3. GENERAL CONSIDERATIONS

Hemodynamic stabilization is guided by the usual clinical assessments of adequate organ and tissue perfusion. Of note, patients with cirrhosis typically exhibit hemodynamic parameters consistent with those of a septic patient.

<table>
<thead>
<tr>
<th>Table 16. Helpful signs of hepatic function in the immediate postoperative period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hemodynamic stability</td>
</tr>
<tr>
<td>2. Awakening from anesthesia</td>
</tr>
<tr>
<td>3. Clearance of lactate</td>
</tr>
<tr>
<td>4. Resolution of hypoglycemia</td>
</tr>
<tr>
<td>5. Normalization of coagulation profile</td>
</tr>
<tr>
<td>6. Resolution of elevated transaminases</td>
</tr>
<tr>
<td>7. Bile of sufficient quantity and golden brown in color</td>
</tr>
</tbody>
</table>
Liver Transplantation

including high cardiac output and low systemic vascular resistance. These hemodynamic conditions may persist for several weeks following transplantation, and may require vasoconstrictive agents for optimal management.

Pulmonary management consists of appropriate ventilatory support with manipulation of respiratory rate, tidal volume, positive end expiratory pressure, and optimal oxygenation. Serial blood gases are used to monitor progress. The patient is typically extubated as soon as he/she is awake and exhibits a good inspiratory effort with adequate vital capacity. Early extubation leads to speedier recovery. However, massive fluid shifts and preoperative generalized debilitation may delay extubation. Once the patient is extubated, careful attention to incentive spirometry and the liberal use of chest physical therapy can help prevent the development of atelectasis and pneumonia. The nature of the incision combined with the state of debilitation of the patient are likely reasons why pulmonary complications are common in the postoperative period. In addition, the common presence of a right-sided pleural effusion in these patients may further delay pulmonary recovery. The importance of pulmonary care following extubation cannot be overstated.

Laboratory testing includes careful attention to glucose levels and electrolyte status. In addition to the usual attention to sodium and potassium, magnesium levels are typically low and magnesium supplementation is required. Ionized calcium determinations should be frequent and ionized calcium should be normalized. In addition, normalization of transaminases and prothrombin time or Factor V levels should be expected in the first 24 hours. If a T-tube is used, the quality of the bile can provide a helpful hint of good liver function. Finally, a baseline doppler ultrasound to assess patency of the hepatic artery in particular should be performed within the first 24 hours of transplantation.

INVESTIGATION OF LIVER FUNCTION TEST ABNORMALITIES

Liver function test abnormalities may consist of elevations in liver transaminases suggestive of hepatocellular necrosis or alkaline phosphatase and bilirubin suggestive of cholestasis. These two patterns of liver function abnormality are not mutually exclusive and can, therefore, occur simultaneously. However, the pattern of liver function abnormality may determine the most appropriate investigation algorithm by suggesting a cause for the laboratory abnormalities. In addition, the timing of the abnormalities may render some causes more suspect than others. The differential diagnosis of abnormal liver function tests include graft dysfunction, technical complications (vascular and biliary), immunological complications (rejection), infectious complications, and finally, recurrence of native disease (Table 17).

Graft dysfunction encompasses a wide spectrum ranging from mild to severe dysfunction. Mild dysfunction is manifested by a significant rise in transaminases postoperatively (above 2,500 IU) as a result of preservation injury. In addition, there may be a second peak in transaminases within 24 hours which is thought to be secondary to reperfusion injury. Regardless of the peak transaminase level, it is important that the trend in transaminase levels be downward. If transaminases continue to rise beyond 12 to 24 hours following transplantation, a more complete
evaluation including assessment of mental status, coagulation profile, renal function, and hemodynamic stability should be carried out (Table 18).

A diagnosis of severe dysfunction or primary nonfunction must be differentiated from that of technical vascular complications including hepatic artery thrombosis, portal vein thrombosis, and hepatic congestion secondary to venous outflow obstruction. Preservation injury is generally associated with improving mental status and stable or improving prothrombin time which is easily correctable. In contrast, primary nonfunction is manifested by a patient who does not awaken and has progressive deterioration of mental status, a worsening coagulation profile which is not correctable, renal dysfunction, and hemodynamic instability. The treatment of severe hepatic dysfunction is primarily supportive. Intravenous prostaglandin E$_1$ has been shown to be beneficial. Bioartificial liver support has been also used as a "bridge" until the liver either recovers or a suitable donor liver is located for urgent retransplantation. In cases of less severe dysfunction, the transaminases normalize over time as do the coagulation parameters. These patients, however, become severely cholestatic in the recovery period, likely as a result of impaired bile transport mechanisms and liver biopsy in these patients may reveal extensive bile plugging with ballooning hepatocyte degeneration consistent with severe cholestasis.

Table 17. Causes of hepatic dysfunction

<table>
<thead>
<tr>
<th>Immediate</th>
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</thead>
<tbody>
<tr>
<td>1. Primary allograft nonfunction</td>
</tr>
<tr>
<td>2. Primary allograft dysfunction</td>
</tr>
<tr>
<td>3. Hepatic artery thrombosis</td>
</tr>
<tr>
<td>4. Portal vein thrombosis</td>
</tr>
<tr>
<td>5. Hepatic vein and caval thrombosis</td>
</tr>
<tr>
<td>6. Biliary tract obstruction/leak</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rejection</td>
</tr>
<tr>
<td>2. Infection</td>
</tr>
<tr>
<td>3. Biliary tract obstruction</td>
</tr>
<tr>
<td>4. Recurrent disease</td>
</tr>
<tr>
<td>5. Graft Dysfunction</td>
</tr>
</tbody>
</table>

Table 18. Signs of primary non-function

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Failure to regain consciousness</td>
</tr>
<tr>
<td>2. Hemodynamic instability</td>
</tr>
<tr>
<td>3. Poor quality and quantity of bile</td>
</tr>
<tr>
<td>4. Increasing prothrombin time</td>
</tr>
<tr>
<td>5. Renal dysfunction</td>
</tr>
<tr>
<td>6. Rise in transaminases and bilirubin</td>
</tr>
<tr>
<td>7. Acid-base imbalance</td>
</tr>
<tr>
<td>8. Persistent hypothermia</td>
</tr>
</tbody>
</table>
**Vascular Complications**

Hepatic artery thrombosis can present with a variety of liver test abnormalities including very subtle elevations in transaminases and, therefore, may go undiagnosed in the early period and become manifest later with biliary complications such as bile leaks, bilomas, liver abscess, and biliary strictures (Table 19).

Therefore, any abnormal trend in liver function tests should be investigated immediately with ultrasound/doppler and, if the hepatic arterial signal is not clearly seen, then an angiogram should be performed. The role of lytic therapy and/or urgent reoperation for thrombectomy remains controversial. Retransplantation may be necessary especially if liver function is severely compromised in the early postoperative period. Hepatic artery thrombosis is usually related to technical complications and, therefore, a satisfactory pulse in the hepatic artery should be obtained before leaving the operating room at the time of transplantation. There is increasing data to suggest that the use of flow probes and the measurement of hepatic artery flow may predict the risk of hepatic artery thrombosis.24

Portal venous thrombosis is less common, but can occur in the setting of significant portal vein stenosis or previous portal vein thrombosis in the recipient, especially in the pediatric recipient. Typically, severe elevations in transaminases are observed in the early period and ascites is a manifestation in delayed portal vein thrombosis. Also, acute portal hypertension manifested by variceal bleeding should alert the surgeon to the possibility of acute portal vein thrombosis. In the acute setting, thrombectomy should be attempted in an effort to save the graft, although retransplantation may be necessary especially if the graft is compromised.

Finally, venous outflow obstruction causing a Budd-Chiari-like congestion of the liver can be seen either following standard hepatic transplantation with end-to-end SVC anastomosis, but has been more commonly described in the setting of piggyback operations. Several innovative techniques have been advocated for repair. In the early postoperative period, a significant elevation in transaminases results from the acute congestion, whereas delayed manifestations consist primarily of ascites and evidence of portal hypertension.

**Biliary Tract Complications**

Anastomotic biliary leaks may occur early in the postoperative period resulting in either localized or generalized peritonitis. Biliary output from the drains and elevation in serum bilirubin out of keeping with elevation in the other liver function tests should raise this diagnostic possibility. These biliary leaks can occur either as a result of technical problems or as a result of hepatic artery thrombosis.

---

**Table 19. Manifestations of hepatic artery thrombosis**

| 1. | Elevation of the transaminases and bilirubin |
| 2. | Fulminant hepatic failure |
| 3. | Sepsis with hepatic abscesses or gangrene of the liver |
| 4. | Biliary anastomotic disruption |
| 5. | Biliary tract strictures |
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with ischemic compromise of the bile duct. These early leaks are best treated by reoperation and revision to a Roux-en-Y choledochojejunostomy. Localized leaks may be treated with endoscopic retrograde cholangiography (ERCP) and sphincterotomy with stenting of the bile duct leak.

Biliary leaks from the raw surface of split livers can be treated conservatively, especially if the leak is contained and adequately drained. If the leak continues, ERCP with sphincterotomy may be necessary. Delayed complications include stenoses of the bile duct anastomosis and intrahepatic biliary strictures which may or may not be related to hepatic artery thrombosis. These are typically managed by skilled ERCP intervention with dilatation and stenting. Where these fail, biliary reconstruction with a Roux-en-Y choledochojejunostomy may be necessary. Finally, dysfunctional motility of the bile duct and of the Sphincter of Oddi may result in functional obstruction in the absence of mechanical obstruction. These types of problems manifest later on in the postoperative period. Also, biliary casts and stones can form, especially in the presence of longstanding T-tubes and may result in biliary obstruction requiring ERCP intervention.

The use of either endoscopic or percutaneous (transhepatic) techniques in the management of biliary complications is dictated by the availability of skilled interventional endoscopists and radiologists at the particular institution. In our opinion, endoscopic (ERCP) intervention is preferred and percutaneous transhepatic procedures are used, when for technical reasons, endoscopic access to the involved biliary tract is not possible.

Rejection

Rejection can occur in the first days following transplantation, especially if induction immunosuppressive therapy is not used. The pattern of liver function test abnormalities varies and can be hepatocellular or cholestatic in nature. Diagnosis is made by liver biopsy since clinical signs and symptoms of rejection are extremely variable, non-specific, and unreliable (Table 20).

Rejection is a common phenomenon with at least 60 percent of liver transplant recipients having at least one episode. Acute cellular rejection usually occurs between the fourth and fourteenth day posttransplant with most episodes occurring within three months of transplantation. Some patients are asymptomatic while others may experience profound symptoms due to a failing liver allograft. The diagnosis of allograft rejection is confirmed by histologic examination of a liver biopsy. Classic histologic findings of acute cellular rejection include a portal infiltrate consisting of mixed inflammatory cells, where the presence of eosinophils

Table 20. Signs and symptoms of rejection

1. Fever
2. Decreased quality and quantity of bile
3. Elevation of the bilirubin and/or transaminase levels
4. Sense of ill being
5. Increased ascites
can be diagnostic, as well as lymphocyte-mediated bile duct injury, and endothelialitis (Fig. 5, Table 21).

**INFECTION**

Abnormality of liver function tests secondary to infection is most commonly secondary to viral infections which include cytomegalovirus (CMV) hepatitis, as well as recurrence of previous viral hepatitis. Recurrence of disease will be covered in the next section. CMV hepatitis is diagnosed by the presence of inclusion bodies with clusters of polymorphonuclear cells (Fig. 6). These “clusters” repre-

![Hematoxylin and eosin stain of acute cellular rejection demonstrating a mixed portal infiltrate with many eosinophils, endothelialitis, and evidence of cellular-mediated bile duct disruption.](image)

**Table 21. Histologic determinants of acute cellular rejection**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (mild)</td>
<td>Cellular infiltrate in a minority (&lt; 50%) of the triads, that is generally mild, and confined within the portal spaces.</td>
</tr>
<tr>
<td>II (moderate)</td>
<td>Cellular infiltrate, expanding most (&gt; 50%) or all of the triads. As above for moderate, with spillover into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis.</td>
</tr>
</tbody>
</table>

![Image](image)
sent the “footprints” of CMV. This evidence of tissue invasive disease is often associated with symptoms of fever, general malaise, myalgia, and diagnosis is corroborated with shell vial culture or positive antigenemia tests. Treatment consists of reduction in immunosuppression and antiviral agents such as ganciclovir. In addition to CMV infection, other bacterial and fungal systemic infections may result in a secondary abnormality in liver function tests associated primarily with a cholestatic pattern. These elevations are difficult to sort out and may require multiple diagnostic efforts. Finally infection of the liver secondary to abscess formation may occur resulting in abnormal liver function tests typically as a result of hepatic artery thrombosis. These can be bacterial and fungal in nature and can be diagnosed first with ultrasound, then CT scan, and finally angiography. ERCP may be helpful in delineating the extent of biliary duct disruption. If severe enough, these biliary tract complications may require retransplantation of the liver.

**Recurrence of Native Disease**

Recurrence of native disease consists most frequently of recurrence of viral infection such as hepatitis B and hepatitis C, as well as non-A, non-B, non-C hepatitis. Recurrence of hepatitis B is easy to diagnose with either serum markers or stains for surface antigen and core antigen on the biopsy. In contrast, recurrence of hepatitis C may be more difficult to differentiate histologically from other causes of liver abnormality such as rejection. Although there is some evidence that there

---

**Fig. 6.** Immunoperoxidase stain of CMV hepatitis demonstrating an inclusion body with intranuclear staining for CMV and a surrounding cluster of polymorphonuclear cells.
may be a role for immune modulators and antiviral agents such as interferon and ribavirin in the prophylaxis and treatment of recurrent hepatitis C, the data are inconclusive. Similarly, recurrence of non-A, non-B, non-C hepatitis can be extremely difficult to diagnose and these patients are often treated mistakenly for acute cellular rejection, which may initially improve liver number abnormalities, but eventually these abnormalities recur. In addition, recurrence of other diseases such as primary biliary cirrhosis, non-alcoholic steatohepatitis, and to a lesser degree, primary sclerosing cholangitis and autoimmune hepatitis have been described. These disease recurrences are typically diagnosed with a combination of liver biopsy and imaging of the biliary tree. The management of recurrence in these diseases can be difficult and for the most part, they are treated much in the same way as in the native liver.

**POSTOPERATIVE CARE**

The aspects and specifics of postoperative care are best delineated according to the particular postoperative period. These periods include: (i) the immediate postoperative, (ii) early postoperative inpatient, (iii) early outpatient, and (iv) long-term outpatient periods.

1) IMMEDIATE POSTOPERATIVE INPATIENT CARE

The bulk of the specifics of the immediate postoperative care are discussed above. The immediate postoperative period is defined by the postoperative intensive care unit stay. However, since immunosuppression is usually instituted in this period, a discussion of immunosuppression as it applies to liver transplantation follows.

**IMMUNOSUPPRESSION**

Induction therapy, traditionally in the form of anti-lymphocyte preparations (MALG, ATG, OKT3), have for the most part, not been widely used in liver transplantation. More recently, a resurgence of interest in induction therapy has resulted from the introduction of humanized IL-2 receptor antibodies (Zenapax and Simulect). The role of these and other newer induction agents in liver transplantation remain to be elucidated.

Baseline immunosuppression is instituted in the immediate postoperative period and typically consists of a calcineurin inhibitor (either Neoral (cyclosporine) or Prograf (tacrolimus)) and steroids. There are very few indications for intravenous administration of calcineurin inhibitors. Steroids are administered initially as intravenous Solu-Medrol and, once the patient is tolerating oral intake with sips of fluids, prednisone is used. Some centers advocate the use of a third agent, historically Imuran (azathioprine). Cellcept (mycophenolate mofetil) which has largely replaced Imuran in kidney and kidney/pancreas transplantation is being used increasingly either as a third agent or in an attempt to obviate the use of steroids, and in some patients the use of calcineurin inhibitors. The role of Cellcept in baseline immunosuppression for liver transplantation remains to be better defined. Rapamycin is presently being evaluated as an additional agent for baseline immunosuppression.
II) EARLY POSTOPERATIVE INPATIENT CARE

Patients are transferred out of the intensive care unit onto the transplant ward as soon as they are extubated and hemodynamically stable. This period is typically 24 to 48 hours and, upon transfer, the patients are encouraged to ambulate. Often, the patients’ pretransplant debilitated state does not allow for early ambulation and these patients require special rehabilitation requiring transfer to acute rehabilitation units. However, if the patients are doing well and do not need long-term rehabilitation care, their diet is advanced as tolerated. Standard wound care is administered and the drains are removed, especially if no biliary leak is evident. Of note, the presence of large volumes of ascites in the drains should not result in delay in removing the drains.

In addition to immunosuppressive agents, prophylaxis against Pneumocystis carinii (PCP) is achieved with Bactrim. In patients with an allergy to sulfa-containing compounds, pentamidine inhalation and dapsone have been used successfully. Cytomegalovirus (CMV) prophylaxis is achieved with ganciclovir therapy. Most centers have transitioned from the use of intravenous ganciclovir preparations to the recently available oral preparations of ganciclovir. Newer preparations of oral ganciclovir appear to have better absorption and bioavailability kinetics and are likely to replace intravenous ganciclovir for prophylaxis. Of concern, increasing resistance to ganciclovir may dictate the use of anti-cytomegalovirus cocktails in the future especially for preemptive therapy rather than prophylaxis.

Standard antibacterial prophylaxis necessitates coverage of gram negative and anaerobic agents typically present in bile. Gram positive coverage appears to be less important. Finally, antifungal prophylaxis is achieved with swish and swallow of nystatin suspension or other such topical antifungal. In addition, agents such as fluconazole and itraconazole are used in the early postoperative period as prophylaxis against systemic fungal infections. Of note, these latter agents can result in dramatic increases of calcineurin inhibitor levels due to competition with cytochrome P450, and therefore, levels need to be monitored closely.

Most patients also receive peptic ulcer disease prophylaxis especially when receiving high-dose steroids in the form of either H2 blockers or proton pump inhibitors. Magnesium supplementation is often necessary in patients who exhibit hypomagnesemia.

In addition to consideration of immunosuppression and prophylaxis, close attention to liver function tests and hematology and biochemistry laboratory values is essential in the first few days following transplantation. Typical problems of thrombocytopenia and mild renal dysfunction may require intervention such as platelet transfusion and optimization of central filling pressures, respectively. Liver function test abnormalities are investigated as outlined above for the immediate postoperative period.

In the case of inability to tolerate oral feedings, enteral feedings via nasoduodenal tube or intravenous hyperalimentation may be important. There are no convincing data to show that routine use of hyperalimentation, either intravenous or enteral, is beneficial in the majority of patients.
Common infections following liver transplantation include urinary tract, pulmonary, intra-abdominal, central venous catheter, and wound infections. Any fever or leukocytosis needs investigation for possible infection in these systems (Table 22).

If a T-tube is used, a T-tube cholangiogram is obtained at approximately the fifth postoperative day and in the absence of leak or obstruction, the T-tube is clamped. Clamping of the T-tube can result in a transient elevation in liver function tests. If the patient develops any abdominal pain following clamping of the T-tube, the house staff should be instructed to unclamp the T-tube and attach it to a drainage bag to gravity immediately. Following this, a repeat cholangiogram or HIDA scan should be obtained to rule out a biliary leak.

### III) EARLY OUTPATIENT CARE

As soon as the patients are tolerating a diet and able to ambulate, they can be discharged to the outpatient setting and followed closely in the outpatient clinic. Typically, blood work is obtained three times weekly and the patients are seen and examined on a weekly basis. A standard protocol for the frequency of laboratory investigations and clinic visits is established (Table 23). Clinic visits are used to evaluate the patient and to review their medications to avoid errors.

Any elevation in liver function tests or any lab work abnormality is investigated further. Standard algorithm for elevation in liver function tests includes an ultrasound doppler examination of the liver looking for patency of the hepatic artery, portal vein, and hepatic veins. Also, the ultrasound will detect any dilatation of the biliary tree and any abnormalities within the parenchyma such as liver abscess formation. If the ultrasound is unremarkable, the next step usually consists of a percutaneous liver biopsy to rule out rejection and infection. In the early postoperative period, especially in patients undergoing transplantation for diseases other than chronic viral hepatitis, elevation in liver numbers can be treated empirically with steroid boluses without a need for biopsy. When needed, biopsies can be performed as outpatients and rejection can also be treated in the outpatient setting. In the case of steroid-resistant rejection which must be documented by a liver biopsy, treatment consists of anti-lymphocyte preparations (OKT3, ATG) typically for two weeks. OKT3 can be administered via peripheral vein, but a cytokine release syndrome may be associated with injection of OKT3 and, therefore, the first two to three doses of OKT3 need to be given in the inpatient setting.

<table>
<thead>
<tr>
<th>Common causes of bacterial infection following liver transplantation</th>
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<tbody>
<tr>
<td>1. Line sepsis</td>
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<tr>
<td>2. Infected peritoneal fluid</td>
</tr>
<tr>
<td>3. Pneumonia</td>
</tr>
<tr>
<td>4. Intra-abdominal abscess</td>
</tr>
<tr>
<td>5. Biliary anastomotic leak</td>
</tr>
<tr>
<td>6. Cholangitis secondary to biliary tract obstruction</td>
</tr>
<tr>
<td>7. Urinary tract infection</td>
</tr>
</tbody>
</table>
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and, therefore, require readmission. These reactions can be mild consisting of fever, diarrhea, and general feeling of malaise with myalgias. Alternatively, OKT3 treatment can be associated with violent reactions consisting of shaking chills, dyspnea, pulmonary edema requiring intubation especially in patients who are volume overloaded, and other manifestations of cytokine release.

ATG administration requires a central venous catheter and does not tend to be associated with overt cytokine release syndrome. When anti-lymphocyte therapy is used, ganciclovir prophylaxis intravenously administered concomitantly has been associated with a decreased incidence of CMV infection. More recently, treatment with high-dose Prograf has been used to reverse acute cellular rejection.

If the biopsy does not reveal the cause for elevation in liver function tests, visualization of the biliary tree is imperative, in order to rule out obstruction. If a T-tube was used, a T-tube cholangiogram can be obtained in order to visualize the biliary tree even in the absence of a dilated biliary duct by ultrasound evaluation. Some centers use cystic duct stents and these also can be injected with radiopaque material in an attempt to visualize the biliary tree. If a T-tube or cystic duct stent is not used, visualization of the biliary tree requires ERCP for both diagnosis and intervention if necessary.

On occasion, despite these diagnostic maneuvers, the reason for elevation of liver function tests remains elusive. In the case of recurrent hepatitis C, the biopsy can be misleadingly normal or show the occasional ‘Councilman Body’ or apoptosis of hepatocytes despite significant elevations in liver function tests. In these cases, conservative management and close observation will eventually reveal the cause for liver function tests abnormality. Not infrequently, repeat biopsies are required before a diagnosis can be established.

The use of routine protocol biopsies is controversial. Although some centers use protocol biopsies in every patient, the occasional findings of histologic rejection in a patient with normal liver function tests and no clinical evidence for rejection can pose a management dilemma. Consequently, most transplant centers have abandoned the use of routine protocol biopsies and rely on either laboratory or clinical abnormalities as a stimulus for liver biopsy and other investigations.

In addition to abnormalities in liver function tests, patients are encouraged to report any potential signs of infection such as fever or chills. If a patient experiences a fever, this is quickly investigated with pancultures for bacterial, fungal,

<table>
<thead>
<tr>
<th>Outpatient Visits</th>
<th>Laboratory Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 4 weeks</td>
<td>0 – 1 months</td>
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<tr>
<td>5 – 8 weeks</td>
<td>1 – 2 months</td>
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<tr>
<td>9 – 12 weeks</td>
<td>2 – 3 months</td>
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<td>3 – 6 months</td>
<td>3 – 6 months</td>
</tr>
<tr>
<td>6 – 9 months</td>
<td>6 – 12 months</td>
</tr>
<tr>
<td>9 months – 1 year</td>
<td>12 – 18 months</td>
</tr>
<tr>
<td>After 6 months, patients are returned to their referring physician.</td>
<td>18 – 24 months</td>
</tr>
</tbody>
</table>
and viral infections including CMV. A chest x-ray is also part of the routine fever workup and, if there is an indwelling central venous catheter, retrograde cultures are also used. Antibiotic therapy is instituted empirically in the immunosuppressed patient while awaiting the results of the cultures especially if the patient appears septic or toxic. Low-grade fevers can be investigated and managed in an outpatient setting, whereas high fevers, especially in a toxic patient, require urgent readmission to the hospital and may require more thorough investigation such as a CT scan of the abdomen to rule out intra-abdominal sepsis.

Side effects of the immunosuppressive agents need to be considered. The most common drugs which result in significant side effects are the calcineurin inhibitors. These side effects include nephrotoxicity, neurotoxicity, hyperkalemia, hypomagnesemia, hypertension, and tremor. Prograf has the additional side effect of inducing new onset diabetes and is more prone to result in GI symptoms of abdominal pain and diarrhea. Both drugs are metabolized through the cytochrome P450 system and, therefore, drugs which increase the effective level include erythromycin and antifungal agents ketoconazole, fluconazole, and itraconazole, as well as calcium channel blockers such as diltiazem, verapamil, and nicardipine. Drugs which decrease levels are primarily the anti-seizure medications in general (phenytoin, phenobarbital, and carbamazepine) and most of the anti-tuberculosis medications such as isoniazid, rifampin, and rifabutin. Twelve-hour serum trough levels are measured and monitored closely and the dosage of these agents is guided by these levels.

Imuran and Cellcept primarily cause leukopenia and, when used, these agents must be adjusted according to the white blood cell count. If the white blood cell count is below 3,000, as a rule, these agents should be held. The use of GCSF and GM-CSF have made leukopenia in these patients much easier to manage. The use of these agents has not resulted in increased rejection.

In patients undergoing transplantation for hepatitis B-related chronic liver disease, human hepatitis immunoglobulin (HBIg) preparations are administered in high doses during the perioperative period. Typically, 10,000 U are administered intravenously during the anhepatic phase and then daily for six to seven days. Titers of antibody are measured and are maintained above 300. At one week following transplantation, the HBIg are administered intravenously weekly at first and then monthly. Eventually HBIg can be administered intramuscularly at monthly intervals always maintaining titers above 300 IU (Table 24). In addition, antiviral agents have been used, particularly in patients with HBV DNA positivity prior to transplant. DNA positivity is considered a contraindication to transplant unless patients can be rendered DNA negative with the use of antivirals such as lamivudine. In patients who are rendered HBV DNA negative with lamivudine, over time, lamivudine-resistant mutants arise and, therefore, the combination of HBIg and lamivudine is thought to provide better recurrence prophylaxis than either agent alone. Lamivudine is continued in the posttransplant period and the optimal combination regimen for HBIg and lamivudine in the long term remains to be worked out.
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Patients who undergo transplantation and are found to have hepatocellular carcinoma (HCC) need close monitoring posttransplantation for recurrence. A large proportion of these patients have elevated alpha-fetoprotein (AFP) levels prior to transplantation and, in those patients, serial AFP determinations can be used to monitor recurrence. Unfortunately, recurrence of HCC is associated with poor long-term outcome. Despite the use of pretransplant adjuvant therapy in the form of either chemoembolization or local therapy, the use of adjuvant chemotherapy following transplantation is not used universally. The treatment of recurrent HCC is not very satisfactory. On occasion, local recurrence at a site of needle biopsy can be excised with no negative impact on survival. However, intra-abdominal recurrence is usually associated with poor long-term survival.

Table 24. Liver transplant protocol for HBV DNA positive patients

1. Pretransplant
   HBV DNA positive patients are to be started on lamivudine 100 mg po q day (available in elixir). If unable to tolerate elixir, it is available in 150 mg tablets; may take 150 mg q day. Recheck Hepatitis B surface antigen, HBV DNA, and Hepatitis Be antigen and antibody at one month intervals for three months. Following two successive negative results, repeat every two to three months. Due to reported cases of pancreatitis using other related drugs, also check amylase periodically. Patient remains on lamivudine.

2. Intraoperative
   Stage II (Anhepatic) – 10,000 IV of HBlg given IV.

3. Postoperative – Inpatient
   A. 10,000 IU HBlg IV daily x 6 days.
   B. Blood samples at trough point (just prior to next dose). Samples to be done on days 1, 2, and 6 and more frequently if necessary based on results (desired level is > 300 IU).

4. Postoperative – Outpatient
   A. If the trough HBV level on day six is > 300 IU, begin giving 10,000 IU IV q week x 4 weeks. At this point, if desired levels are maintained, can switch to 5cc HBV IM q week x 4 weeks. If desired levels are still maintained, can switch to 5cc HBV IM q month.
   B. Laboratory monitoring:
      Hep B surface antigen         q month x 3 months
      Hep Be antigen               then, q 3 months x 12 months
      Hep Be antibody
      HBV DNA
      HBV levels (trough)          q week x 3 months
                                   then, q 2 weeks x 3 months
      HBV DNA quantitative         q 3 months x 12 months

5. Long-Term Monitoring
   If patient remains HBV DNA negative after 6 months, obtain HBV levels q month. Continue administering 5 cc HBV IM q month for at least the first year. Longer term dosing and laboratory monitoring will depend on patient response and broader experience data. Patient is to remain on lamivudine for lifetime.
Long-Term Outpatient Care

Once the patient has overcome the problems that characterize the first three to six months after transplantation, such as acute rejection and infection, new diagnostic and therapeutic goals become important. Some are directly related to transplantation, such as the progressive reduction in the dose of immunosuppressive agents and the periodic surveillance of liver function tests to screen for late complications. Others require a focus on the potential for complications that may arise from medications including the immunosuppressive agents. This longer term follow-up requires special attention to six major areas.

i) Liver function tests: Disease recurrence is possible following transplantation for certain indications. Reinfection of the liver after transplantation is common with hepatitis C, which may progress slowly to a fibrotic/cirrhotic stage in a smaller group of patients (10%) over a 2-5 year period. Reinfection with hepatitis B can progress more rapidly to a potentially fatal course with a picture of fibrosing cholestatic hepatitis; patients require active measures to prevent reinfection (e.g., hyperimmunoglobulin) and viral replication (e.g., lamivudine). Recurrence of primary biliary cirrhosis has been documented, although histological overlap with chronic rejection may confuse interpretation.

ii) Arterial blood pressure: The administration of calcineurin inhibitors and corticosteroids may result in arterial hypertension in up to 70% of transplant recipients. Sympathetic stimulation with attendant vasoconstriction and volume expansion are thought to be responsible. In addition, liver disease prior to transplantation, characterized by systemic vasodilatation may “protect” the hypertensive patient. The need for calcium channel blockers (with attention to possible interactions with cyclosporin/tacrolimus), selective and non-selective beta blockers and diuretics is commonly seen in patients following liver transplantation. Decreasing the doses of calcineurin inhibitors and/or steroids may help reduce the need for antihypertensive agents.

Renal function: Deterioration of renal function is common after liver transplantation, mainly as a result of the sympathetic stimulation, renal vasoconstriction and decrease in glomerular filtration rate induced by calcineurin inhibitors. A reversible reduction in creatinine clearance of approximately 50% can be seen at one year. Over a more prolonged period, permanent reductions in renal function may occur, with variable degrees of proteinuria. Histology reflects both ischemic injury to the glomerulus as well as tubular damage. The use of prostaglandins has not been shown to diminish calcineurin-induced nephrotoxicity. In addition, the use of non-steroidal antiinflammatory agents and the use of drugs which affect the metabolism of calcineurin inhibitors can both result in impaired renal function.

Metabolic issues: Chronic liver disease is an insulin-resistant state and the administration of corticosteroids after the transplantation may result in overt diabetes. In addition, tacrolimus has been demonstrated to be diabetogenic irrespective
of steroids. Elevations of both serum cholesterol and triglycerides can occur with cyclosporin, which may be somewhat less pronounced with tacrolimus. Drugs which affect cholesterol production have been used effectively in patients with elevated lipids. Hyperuricemia with gouty attacks reflect an effect of cyclosporin. Weight gain after transplantation can be substantial, especially after the 2nd month. Hyperphagia, high steroid dosage and central effects of calcineurin inhibitors contribute to this effect. Excessive weight gain has adverse repercussions on the control of blood pressure and diabetes. Development of atherosclerotic vascular disease is of concern and every effort should be made to control these metabolic effects, especially hyperlipidemia and diabetes.

Bone disease: Prior to liver transplantation, patients with chronic liver disease often have underlying bone disease, especially those individuals with cholestatic liver disease and those receiving steroids for autoimmune hepatitis. Bone loss occurs primarily in the first six months after transplantation and active measures to prevent this deterioration should be instituted. Baseline bone densitometry is of assistance to guide replacement. The latter includes supplementation with calcium and vitamin D. Anti-resorptive therapy with biphosphonates should also be considered.

Screening: It is important to be proactive in the search for potential complications. This includes periodic ophthalmological exams to rule out glaucoma and cataracts. Screening for malignancy proceeds under similar protocols to the general population, including mammography, gynecological examination and colonoscopy. Some additions exist as a result of the immunosuppressive state. Careful dermatological examination is important at every visit, as there is an increased incidence of squamous cell carcinoma of the skin. Patients should avoid bright sunlight hours and use sun-protecting lotions. Patients with primary sclerosing cholangitis and ulcerative colitis may be at high risk for development of colon carcinoma. Post-transplant lymphoproliferative disorder has a wide spectrum of pathology and can respond well to a reduction of immunosuppression. Knowledge of the rates of de novo malignancies following transplantation can be a useful guide to screening in these patients.

Psychological well-being: Well adjusted patients should resume their pre-transplant activities, retain gainful employment, and maintain normal social interactions. The transplant evaluation process should detect any warning signals which suggest a lack of motivation. Depression should be diagnosed as should other important factors such as personality disorders. Issues of compliance and recidivism, especially in patients with alcoholic liver disease cannot be overemphasized. This evaluation should include nursing, social work, and psychiatric services as needed. Vocational rehabilitation may be necessary. Finally, quality of life assessments should routinely be performed by transplant centers.
Overview

Over the past decade, the gap between the number of adult patients in need of liver transplantation and the number of organs donated has increased greatly. This discrepancy has increased both the mean waiting time to undergo transplant and mortality from complications of end-stage cirrhosis for patients on the waiting list. Over the past several years, attempts to address the inadequate supply of organs for transplant have included the use of marginal donors (age, hemodynamics, viral infection). More recently, living donors have been used to address this need.

The concept of using a living donor developed in pediatric transplantation more than a decade ago, waiting list mortality declined, and the procedure was shown to have excellent recipient results and low risk for morbidity and mortality in the donor. This concept was extended to adult live-donor liver transplant (LDLT). The LDLT procedure involves transplantation of the right hepatic lobe from one adult donor to another, with the first series in the United States presented in 1998.

Live-Donor Liver Transplant Recipient

LDLT is considered for those patients likely to experience mortality while awaiting a cadaveric organ donor. Table 26 outlines those patients who are candidates for LDLT.

Donor and Recipient Procedure

The donor procedure consists of a formal right hepatic lobectomy with extreme care to avoid injury to those structures servicing the residual liver, or left lobe. Intraoperative cholangiogram and ultrasound is often necessary in this regard. Once harvested, the lobe is flushed with preservative solution and, if necessary, vascular reconstruction is completed on the back table in preparation for implantation. The recipient operation involves an IVC-sparing hepatectomy with anastomosis of the donor right-sided structures (vascular, biliary) to the corresponding recipient structures. LDLT provides an alternative which may reduce the waiting-list mortality in selected patients. Ongoing studies will determine the true risk to the donors and whether recipient outcomes are comparable to whole liver transplant.

Liver Transplantation - A New Era

Approximately 10,000 liver transplants have been performed to date, mostly in the post-cyclosporine era. For the most part, one-year and five-year patient survival rates are 90 percent and 75 percent, respectively. Graft survival rates may be slightly lower reflecting an incidence of retransplantation. Quality of life studies have shown that most patients have an excellent quality of life following trans-
Liver and Intestinal Transplantation

Although the long-term care of the immunosuppressed patient is an evolving field which presents many interesting challenges. Certainly, chronic side effects of immunosuppressive therapy, de novo malignancies, and recurrence of native disease continue to present significant problems. These important clinical entities form the basis for present and future research in transplantation.

There has been a dramatic shift in the paradigm of liver transplantation in the last decade. Long-term results are unequivocally excellent and there is no longer a need to convince other clinicians that liver transplantation is a worthwhile therapeutic entity. Currently, our most significant hurdle includes a prohibitive organ shortage with resulting ongoing disagreements about allocation. Although living donor transplants have become increasingly utilized in both pediatric and adult recipient, the discrepancy between the need and the supply of organs continues to widen. Until xenotransplantation becomes a clinical reality, live donors will be used increasingly. The inherent risk to the donor requires a meticulous assessment of both clinical and ethical issues. Therefore, it behooves the transplant community to monitor closely the results of adult-to-adult living donor liver transplantation, although the long-term care of the immunosuppressed patient is an evolving field which presents many interesting challenges. Certainly, chronic side effects of immunosuppressive therapy, de novo malignancies, and recurrence of native disease continue to present significant problems. These important clinical entities form the basis for present and future research in transplantation.

Table 26. LDLT candidate recipients

<table>
<thead>
<tr>
<th>A. Pre-MELD</th>
<th>B. Post-MELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular carcinoma (T1 and T2)</td>
<td>Hepatocellular carcinoma (exceeding T2 criteria)</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>Complications of cirrhosis, low MELD score</td>
</tr>
<tr>
<td>Patients not likely to receive cadaveric organ with life expectancy less than 6 months</td>
<td>GI bleeding</td>
</tr>
<tr>
<td></td>
<td>Hepatic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Intractable pruritus</td>
</tr>
<tr>
<td></td>
<td>Recurrent cholangitis</td>
</tr>
<tr>
<td></td>
<td>Fulminant hepatic failure</td>
</tr>
</tbody>
</table>

Donor Candidacy and Evaluation

Potential donors are evaluated by a donor advocate team, must be complete healthy, and have hepatic size and anatomy compatible with right lobe transplantation (Table 27).

Table 27. Right lobe donor evaluation

<table>
<thead>
<tr>
<th>History and physical exam (donor advocate physician)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosocial evaluation (social work, psychiatry)</td>
</tr>
<tr>
<td>Laboratory assessment</td>
</tr>
<tr>
<td>CBC, chemistry, coagulation profile</td>
</tr>
<tr>
<td>Thrombophilia screening, viral serologies (HIV, HBV, HCV, etc.)</td>
</tr>
<tr>
<td>ECG, chest radiograph</td>
</tr>
<tr>
<td>Cardiac stress testing, if indicated</td>
</tr>
<tr>
<td>Liver imaging (MRI, MRA, MRV, MRCP, or CT scan/ERCP)</td>
</tr>
<tr>
<td>Liver biopsy, if indicated</td>
</tr>
<tr>
<td>Family agreement/consent, no evidence of compensation/coercion</td>
</tr>
</tbody>
</table>
transplantation, as well as donor morbidity and mortality. This effort will require funding from the Federal Government so that appropriate registries can be supported. Finally, the resulting longer waiting times will necessitate more aggressive and innovative management algorithms for the complications of cirrhosis.

**REFERENCES**


Liver transplantation in children shares many similarities with that in adults. There are, however, important differences. The diseases which lead to liver insufficiency in children are dissimilar, and the interval between diagnosis of liver dysfunction and rapid deterioration in health due to liver disease is often more compressed in the child as compared to the adult. Liver disease in infancy interferes with the critical period of growth and development in the early years of life and adds to the urgency of transplantation so that losses can be regained. In the following chapter, we have concentrated on the areas in which the management of children before and after transplantation differs most from that in older patients.

**CAUSES OF LIVER FAILURE UNIQUE TO CHILDREN**

The most common indication for liver transplantation in children is Biliary Atresia. Biliary Atresia is a progressive fibro-inflammatory destruction of the extrahepatic biliary tree, which develops in approximately 1 in 15,000 newborns. The etiology of the disorder remains unknown, but as many as 10% of affected children will have associated developmental abnormalities such as polysplenia, malrotation, and intra-abdominal vascular anomalies. Some infants will benefit from the Kasai procedure but the majority will have progressive biliary cirrhosis despite surgical intervention. Metabolic liver diseases that result in cirrhosis, such as alpha-1-antitrypsin deficiency and Wilson’s disease, are also common indications for liver transplantation in children. Approximately 5% of the children receiving liver transplants have fulminant hepatic failure. Inborn errors of metabolism without cirrhosis such as Crigler-Najjar syndrome or Ornithine transcarbamylase deficiency are uncommon but important indications as well. Liver transplantation can be performed in children with malignancy, which is limited to the liver such as hepatocellular carcinoma or hepatoblastoma.

**RECIPIENT EVALUATION, SELECTION CRITERIA, LISTING PROCESS**

Patients with chronic liver disease are not actively listed for transplant unless they are judged to have less than six months life expectancy. Predicting life expectancy is dependent upon the form of liver disease. Biliary atresia, for example, has a very predictable progression. Patients who do not have successful biliary drainage following the Kasai procedure invariably reach endstage liver disease with hepatic insufficiency by two years of age. It is best to proceed with transplantation.
when they begin to have linear growth failure and the first complications of portal hypertension. Patients with familial cholestatic syndromes, which ultimately lead to cirrhosis, may have a less predictable course. Growth failure is characteristic of these syndromes even when liver function is preserved. Signs of advancing portal hypertension and liver synthetic failure are the earliest indications for transplant in this group. Children with metabolic defects, which are corrected by transplantation, are approached with a different strategy. In this setting, the goal should be to perform the transplant before the patient develops significant complications from the metabolic defect. The child with fulminant hepatic failure should undergo transplant as soon as a suitable organ is available, since fewer than 25% of these patients will survive without transplant. Table 1 summarizes the medical complications that indicate the need to proceed with transplant.

The preoperative evaluation of a child awaiting liver transplantation includes, establishing the etiology, predicting the timing of the need for transplant, and identifying anatomic abnormalities or other organ system impairment, which would complicate the surgical procedure. Children with cirrhosis should show signs of hepatic insufficiency, such as growth failure or coagulopathy, or have significant complications of portal hypertension, such as ascites or variceal bleeding before liver transplant is performed. A child who has not developed these complications may have many years of good quality of life prior to the need for liver transplant.

Table 1. Medical complications indicating the need for liver transplantation in pediatric patients

<table>
<thead>
<tr>
<th>1) Biliary Atresia</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Status post failed Kasai procedure</td>
</tr>
<tr>
<td>b) Recurrent ascending cholangitis</td>
</tr>
<tr>
<td>c) Complications of cirrhosis as listed below</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2) Cirrhosis of any etiology with the following complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Growth failure</td>
</tr>
<tr>
<td>b) Ascites which is refractory to medical management</td>
</tr>
<tr>
<td>c) Episodes of variceal bleeding which are refractory to sclerotherapy and/or TIPS</td>
</tr>
<tr>
<td>d) Hypersplenism causing thrombocytopenia</td>
</tr>
<tr>
<td>e) Liver synthetic failure</td>
</tr>
<tr>
<td>f) Other major systemic complications</td>
</tr>
</tbody>
</table>

| 3) Fulminant hepatic failure |

| 4) Neonatal liver failure |

<table>
<thead>
<tr>
<th>5) Inborn errors of metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Tyrosinemia</td>
</tr>
<tr>
<td>b) Glycogen storage disease</td>
</tr>
<tr>
<td>c) Crigler-Najjar Syndrome</td>
</tr>
<tr>
<td>d) Ornithine transcarbamylase deficiency</td>
</tr>
<tr>
<td>e) Other defects with the potential to cause neurologic or other major systemic complications</td>
</tr>
</tbody>
</table>

| 6) Unresectable hepatic tumors without extension |
ANESTHETIC CONSIDERATIONS

Children present anesthetic challenges different from those in adults, but those under 10 kg in size present unique anesthetic considerations. Intravenous access is best secured with a large single lumen tunneled catheter directly into the internal jugular or subclavian vein. Large bore catheters are essential for adequate fluid and blood replacement since babies have small circulating volumes which are rapidly depleted in the face of ongoing hemorrhage. In addition to a fluid replacement catheter, a double lumen central catheter is also desirable for drug administration. An arterial line is also essential. Tunneled catheters provide long term IV access in infants who may otherwise present great difficulties in drawing blood or starting IVs as outpatients.

Heat preservation may be a problem in small children who are often hypothermic during a long transplant. Devices to direct warm air along the body of an infant are very helpful in maintaining core temperature above 35° during the operation. Rapid infusion systems should be available if blood loss is anticipated to be heavy. Cell saver devices are impractical in children less than 10 kg in size because of the relatively small volume of blood lost in these children.

It is useful to have at least two anesthetists who are experienced in the care of children during a transplant operation. One set of hands, however knowledgeable, may not be sufficient to deal with the many tasks that are necessary for a successful anesthetic. Blood monitoring for blood gases, serum electrolytes, calcium, magnesium and blood counts should be done at least once per hour, even in stable situations. Monitoring of coagulation parameters is essential for the management of the bleeding complications often seen during a liver transplant. A thromboelastogram device may be helpful in pinpointing a coagulation defect in the face of ongoing bleeding with abnormal bleeding times.

TRANSPLANT PROCEDURE AND INTRAOPERATIVE CONSIDERATIONS

Operative techniques in pediatric liver transplantation have evolved significantly in the last decade. The most important advances include the techniques to reduce the size of a large donor’s liver in order to transplant a portion into a small child, the procurement of grafts from living donors and the division of a liver to transplant into a child and an older recipient.2

The transplant operation itself can be divided into three phases: the removal of the native liver, the anhepatic phase during which the new organ is implanted, and the reperfusion phase.

EXPLANT OF DISEASED LIVER

The removal of a diseased liver in the child is often the most hazardous part of the liver transplant procedure. Much of the dissection is done with cautery to minimize bleeding or with sharp dissection with ligation of all structures that will be divided. Patients with previous Kasai operations for biliary atresia have extensive scarring in the right upper quadrant increasing the difficulty of dissection.3
After opening the abdomen, adhesions between the liver, colon, stomach and abdominal wall obscure clear entry into the abdominal cavity. The portoenterostomy must be traced into the hilum and divided close to the liver in order to access the hepatic artery and portal vein. The hepatic artery and portal vein must be divided close to the liver beyond their bifurcation in order to preserve length. Patients with biliary atresia will often have unusual anatomical features such as preduodenal portal vein, retroperitoneal continuation of the inferior vena cava, left sided vena cava and situs inversus abdominis. Anatomical anomalies are common and are not always diagnosed with pretransplant imaging.

Long standing portal hypertension may contribute to progressive shunting of mesenteric blood away from the liver leading to hypoplasia of the portal vein. In extreme cases the portal vein size is less than 2 mm in diameter and flow is minimal and makes the portal vein unsuitable for use as a conduit of mesenteric blood to the new liver. One must trace the portal vein to the confluence of the splenic and superior mesenteric veins where the flow of blood is acceptable. Vein grafts from the donor may be used to bridge the distance between the native vein and the donor liver. In pediatric transplantation, the native inferior vena cava is often left in place. The vena cava is mobilized completely, but the adrenal vein is preserved. Retrohepatic branches may be ligated and divided individually. Alternately, clamps can be placed above and below the liver on the IVC and the liver dissected sharply off the vein. Vein branches can then be oversewn under direct vision.

Implantation of the New Organ

Over 50% of infant transplants are done with organs that have been reduced in size from older donors. These include size reduced cadaveric organs, split livers where the right lobe is preserved for transplantation into another recipient, and living donor procured segments.

Cadaveric organs that are reduced in size for a single recipient only, are reduced in size on the back table. When the donor’s weight is less than four times that of the recipient, the entire left lobe can usually be transplanted. All structures to the right lobe are divided and ligated. The parenchyma is then divided in the plane of the inferior vena cava and gall bladder. Particular attention must be paid to the area of the confluence of the hepatic veins to insure that all major veins are secured. If the donor is more than four times the weight of the recipient, the size of the liver will only permit implantation of segments 2 and 3. Parenchymal division takes place to the right of the falciform ligament.

For organs that are considered for transplantation into two recipients, the division of the liver can be done either in or ex vivo depending on the logistics of the transplant, cold ischemic time, and preference of the teams. Important technical features in splitting a liver are preservation of segment 4 arterial supply, division of the bile duct preferably beyond the confluence of the segments 2 and 3 ducts, and preservation of as much of the length of the left portal vein. Hepatic venous anomalies are uncommon. The left hepatic vein is usually sufficient to provide adequate venous drainage of segments 2 and 3 or even the entire left lobe.
When the operative field is ready for implantation, the graft is positioned in such a manner as to facilitate proper portal vein orientation. If the liver is piggybacked onto the cava, the venous orifices of all 3 hepatic veins may be used as a single confluence to ensure proper venous drainage of the graft. Alternately, a new caval orifice can be created more inferiorly on the vena cava orienting the liver more medially, and allowing the portal vein ends to come together with less tension. Fine absorbable monofilament sutures are used for the venous anastomosis. The artery is anastomosed using fine interrupted nonabsorbable sutures and an operating microscope in infants or when the donor vessels are small such as in living donor transplants.

**Reperfusion Phase**

After reperfusion, a number of metabolic changes occur. Calcium requirements decrease or stop, the serum bicarbonate level rises and potassium may fall. Additionally, PTT may go up. The coagulopathy may require additional fresh frozen plasma, but more aggressive coagulation factor replacement with cryoprecipitate is not advisable unless bleeding is life threatening. Over correction of the coagulopathy seen after reperfusion may lead to hepatic arterial thrombosis.

During this last phase, the Roux loop is constructed if necessary, and the bile duct anastomosis is completed.

Children usually require biliary reconstruction using a Roux loop of bowel. The choledochojejunostomy is done over a stent in cases of very small ducts in order to ensure that the back wall is not accidentally included in the front wall reconstruction. In cases of grafts from living donors or where the liver is split, separate ducts from segments 2 and 3 may be encountered which require individual attachment to the bowel.

**Recovery and Intensive Care**

The postoperative phase of care is characterized by careful monitoring for graft function, fluid replacement and electrolyte monitoring. Portal vein and hepatic arterial flow is also monitored by ultrasound. Some bleeding is not infrequent in the postoperative period but does not often require urgent re-operation. Progressive abdominal distention resulting in difficulty in ventilation or decreasing urine output may indicate that a return to the OR is indicated for evacuation of blood and clots. Some form of antithrombosis prophylaxis therapy is desirable. We use a heparin infusion at 10 units/kg/hour as prophylaxis against arterial thrombosis and replace drain output with fresh frozen plasma in infants to correct the hypercoagulable state that may exist following transplantation.

Ultrasound examination is carried out on the first postoperative day to examine arterial and portal venous flow. In the absence of satisfactory flow in either vessel, an immediate return to the operating room is indicated for revision of the vascular anastomoses. Arteriography is rarely necessary to confirm ultrasound findings. Vessels, particularly the portal vein can frequently be revised to restore satisfactory blood flow. Although the success of intervention in cases of arterial occlusion is less predictable, a substantial proportion of these vessels can be opened
up with a combination of thrombolytic therapy in the OR, postoperative anticoagulation and careful revision of the anastomoses to exclude technical factors.\textsuperscript{13}

Arterial hypertension in the ICU is common and can usually be managed by careful fluid management, diuretic therapy and calcium channel blockers. Prophylactic antibiotics are continued for 48 hours usually, and anti CMV prophylaxis is implemented in cases where the donor is CMV positive.\textsuperscript{14}

Patients may be ventilator dependent for a few days following transplantation. Failure to wean from ventilator support is usually secondary to abdominal distention, but intra thoracic pathology should also be suspected. Diaphragmatic dysfunction on the right side from phrenic nerve clamp injury should be suspected when there are no other obvious causes for ongoing ventilator dependence.

**IN-PATIENT CARE AFTER ICU**

**FEEDINGS**

Feedings are generally restarted between the third and fifth post-operative day depending on whether bowel surgery has been performed as part of the transplant. Babies may require feeding tube supplementation particularly when oral intake was poor prior to the transplant. Unless there are complications, the diet can be quickly advanced to age appropriate food supplemented in some cases with special liquid enteral feeds.

**IMMUNOSUPPRESSION**

The resolution of postoperative ileus and implementation of oral feeding calls for vigilance in the monitoring of immunosuppressive medication levels as absorption of these drugs may increase significantly in the days following transplantation. Usually, the transition between intravenous and oral administration of medication takes place during this week unless other complications arise.

**INFECTIONS**

If infections occur in the early postoperative period, they are usually bacterial. Sources of infection include intra abdominal sites such as the bowel or biliary tract, particularly in children who have been transplanted for biliary atresia. Other common sites are intravenous catheter and arterial infusion sites.

Early and aggressive investigation and treatment are essential for the successful resolution of these infections. Careful physical examination, chest X-ray and abdominal ultrasound along with culture of blood, urine and wounds will usually uncover the source. Empirical treatment with antibiotics is often recommended when the source of the fever is undetermined. Antibiotics, which cover enterobacter and enterococci, are important in the early post transplant period. Yeast infections should always be suspected if a septic picture continues and there is no improvement with antibiotics. Children, who have been on pre transplant steroids, those with bile leaks or bowel perforations and those with arterial thrombosis have been shown to be at higher risk for the development of *Candida* infections.
SPECIAL CONSIDERATION FOR IMMUNOSUPPRESSION

The choice of immunosuppressive therapy for a child must balance the need to prevent rejection against the desire to allow normal growth and development and to avoid infectious complications. The approach to therapy in pediatric liver transplantation has largely been adapted from adult experience. Most centers use a triple drug regimen, which includes cyclosporine, azathioprine and corticosteroids. A new oral formulation of cyclosporin has improved intestinal absorption even in the setting of poor bile flow.13,16 This is particularly valuable for small infants who typically require large doses of cyclosporine secondary to poor intestinal absorption. Cyclosporine is usually administered intravenously during the initial postoperative period, but the oral preparation can be absorbed adequately even on the first postoperative day. The cyclosporine dose is adjusted to yield a 12-hour trough level of 250-350 ng/ml as measured by TDX. Azathioprine is administered at a constant dose of 1 mg/kg/day and methylprednisolone or prednisone doses are gradually tapered from 2 mg/kg/day to .3 mg/kg/day over the first month. Tacrolimus is gaining acceptance as an alternative to cyclosporine in pediatric liver transplant recipients. Because it is more potent than cyclosporine, patients treated with tacrolimus are less dependent on steroid administration, and may avoid steroid related complications, such as growth failure and hypertension. Unfortunately, tacrolimus can be difficult to administer to smaller children since it is not available in a liquid formulation. It does not cause the cosmetic side effects associated with cyclosporine, but it may contribute to anorexia and chronic gastrointestinal symptoms, which are not common in children treated with cyclosporine. There is also a growing concern that post transplant lymphoproliferative disease (PTLD) is more common in children who have received tacrolimus.

The use of monoclonal antilymphocyte antibodies, such as OKT3, either for induction or for treatment of steroid resistant rejection is becoming less common in pediatrics since this therapy has also been identified as a risk factor for PTLD.17 Chimeric antibody preparations for specific T-cell markers are being tested in pediatric solid organ recipients and may prove to be safe and effective alternatives to current antilymphocyte therapy.

ASSESSMENT OF GRAFT FUNCTION, DIAGNOSIS AND TREATMENT OF REJECTION

Allograft rejection occurs in approximately two thirds of children following liver transplantation. The peak incidence of acute rejection is within the first 2–6 weeks following the transplant. Fever, jaundice and abdominal pain are typical symptoms at presentation. Frequent monitoring of biochemical indicators of cholestasis and hepatocellular injury may allow the clinician to suspect rejection prior to the onset of typical physical signs. Since the laboratory and physical signs are not specific for rejection, the diagnosis of rejection must always be confirmed by histology. Rejection episodes are treated in a step-wise fashion. The first step is an intensified steroid regimen, which includes intravenous boluses of methylprednisolone (10-20 mg/kg/day for 3 days) occasionally, followed by tapering doses of
oral steroids. If there is no improvement in the biochemical parameters or the liver histology, the next step in treatment might be an antilymphocyte preparation such as OKT3, or conversion from cyclosporine to tacrolimus. Chronic rejection can occur either following an episode of refractory acute rejection or de novo weeks to months after transplant. Chronic rejection is characterized by a slow progression of the clinical signs of cholestasis without many constitutional symptoms. Tacrolimus may be effective in reversing this progression. Although rejection is commonplace, less than 10% of children lose their liver to chronic or ongoing acute rejection.

**DIAGNOSTIC RADIOLOGY**

**PLAIN FILMS**

A preoperative chest film is always done to exclude significant pulmonary disease that may be a contraindication to proceeding with transplantation.

In the postoperative period, evaluation of the abdomen and chest with plain radiographs is done to exclude pleural effusions, pneumonia, pulmonary edema and intraabdominal free air. Bowel perforations may show few overt clinical signs, and careful evaluation of abdominal plain films may provide the first evidence of unusual air or fluid collections that may indicate intestinal or biliary anastomotic dehiscences.

**ULTRASOUND**

The single most useful radiological test in pediatric liver transplantation is the abdominal ultrasound.

Posttransplant day 1 ultrasound is essential for determining the early patency of all vascular anastomoses. The quality of ultrasound studies has improved dramatically over the last several years and obviates the need for angiograms in most cases to confirm arterial or portal venous occlusion. Doppler studies now can provide information about the velocity of flow in vessels as well as the resistive index in the hepatic artery. This information, while not always helpful, may provide the basis for future advances in the evaluation of vascular anastomoses.

Ultrasound also provides information regarding the presence of fluid collections. It may serve as the definitive study to determine the size and nature of a fluid collection, but CT scanning usually is more helpful in determining the need for further interventions or treatment.

**COMPUTERIZED TOMOGRAPHY**

CT scanning gives a wealth of information on the anatomic state of the liver. Periportal edema is a common finding after transplantation and can persist for weeks. Fluid between the left lobe and the stomach or behind the cut surface of the liver is also common and does not necessarily signify infection.

CT scanning is the most definitive study in the investigation of fever. Fluid collections detected by ultrasound can be studied in greater detail with CT. Liver parenchymal lesions are seen in great detail on CT, including perfusion defects, intrahepatic fluid collections and bile duct dilatation.
INTERVENTIONAL RADIOLOGY CONSIDERATIONS

Interventional radiology (IR) has become a full partner in the management of many post transplant issues.

Aspiration of intraabdominal fluid collections to rule out infections is the most common reason for consultation with IR. The decision to go on to surgical drainage can then be taken depending on the outcome of the aspiration and the nature of the fluid.

Investigation of the biliary tract is an area where IR has had a very positive impact. The biliary tree is relatively inaccessible in many children because of the biliary enteric anastomosis usually present. Percutaneous transhepatic cholangiography (PTC) can provide information regarding biliary strictures, leaks, bile cultures and most importantly provides an opportunity for possible corrective measures.

Transhepatic insertion of biliary stents has provided long term and in many cases permanent correction of postoperative biliary strictures. Balloon dilatation of strictures and passage of indwelling stents provide both short and long-term palliation and even permanent solutions to biliary strictures. Stents may be left in place for 8-12 weeks after which they may be removed. Repeated dilatations may be necessary. Placement of permanent stents in the biliary tree has been attempted but long term results have not been gratifying because of the build up of sludge in these stents with resulting obstruction and sepsis.

Vascular interventions are less common. Diagnostic arteriography and venography following transplantation have become less often used as the diagnostic accuracy of ultrasound has improved.

Arterial infusion of thrombolytic agents has been used to treat arterial thrombosis with little to support further use of this technique. Venous obstructions however have been successfully approached through interventional radiology.

Posttransplant portal vein and hepatic vein stenoses have been successfully treated by using transhepatic or transvenous introduction of balloon dilators followed in some instances by placement of permanent indwelling vascular stents. Long term patency of portal veins treated for stenotic areas has been well documented. Hepatic vein lesions may be more difficult to treat because of the confluence of the hepatic veins with the inferior vena cava making stent placement more difficult.

EARLY SURGICAL COMPLICATIONS

BLEEDING

Posttransplant bleeding, when it occurs, is usually slow but persistent. Bleeding into the abdomen occurs to some degree in most transplant patients and postoperative transfusion is often required. Blood is evacuated through the drains left in place at the time of the transplant, but blood and blood clots can occlude the drains and still accumulate in the abdomen resulting in progressive distension. A return to the OR is indicated when abdominal distension interferes with ventilation, renal perfusion and lower limb perfusion. Laparotomy results in the immediate
improvement in renal perfusion and ventilation. The bleeding point, if found, will usually be a small arterial branch in the hilum of the liver or along the course of the hepatic artery. Bleeding is more frequent in reduced size or split liver transplants, but requires laparotomy in less than 10% of cases.

**Nonfunction**

Primary nonfunction occurs in less than 5% of cases, but requires urgent retransplantation when it is diagnosed. Reduced size and split liver transplantation may result in a higher incidence of nonfunction. Therefore, more stringent criteria are used for selection of livers to be reduced in size or split than for those used as whole organs. In general, organs intended for splitting or size reduction must be from donors less than 40 years of age, with near normal enzymes and less than 10% fat.

**Vascular Thromboses**

Early re-exploration of clotted arteries has not been reported to be as successful in children as in adults. Takedown of the arterial anastomosis, infusion of urokinase into the graft and trimming back both the donor and recipient ends of the artery can result in restoration of arterial flow on occasion and is probably worth doing in all cases when the thrombosis is detected early. Microvascular surgical techniques have resulted in a decrease in thrombotic complications in small children. When the artery does clot, however, the clinical course can be unpredictable. Retransplantation is always necessary if significant biliary damage has occurred. Some children, however, have acceptable liver function and heal any ischemic damage with few or no serious sequelae.

**Portal Vein Occlusion**

Unlike arterial thrombosis, portal vein occlusion can almost always be reversed when diagnosed early. Localized thrombus, kinking of the vein, or extrinsic compression can usually be reversed. Even if liver function is acceptable, the portal vein should be declotted to prevent the long-term problems of portal hypertension and cavernous transformation.

**Biliary Problems**

Choledochojunostomies are the most common form of biliary hook up in children. Serious biliary leaks may signify arterial thrombosis, and in that setting, retransplantation may be the most practical option. Operation and evacuation of infected collections, attempted repair of biliary dehiscences and insertion of drains must be done in all cases of bile leaks associated with fever and a septic clinical state. Small leaks, which appear to be adequately drained, may be safely observed even if the artery is not open.

Bile leaks may also originate from secondary ducts that may not be visible at the time of the transplant. Although this may occur with whole liver transplantation, it is more common after living related or split liver transplantation when small segmental ducts at the liver parenchymal transection plane either at the cut
surface or within the liver plate secrete bile into the abdominal cavity. Small ducts at the cut surface may safely be oversewn. Those at the plate may signify segmental ducts and should be anastomosed to the bowel with a separate choledochojunostomy.

**Intestinal Perforations**

Bowel injuries from cautery burns may become evident during the first postoperative week. Leukocytosis and abdominal distention should always raise the possibility of an occult perforation. Leaks from bowel anastomotic suture lines or from de novo perforations in areas not subjected to extensive dissection may also occur. Early diagnosis is essential to prevent recurring infected collections. When the abdominal cavity is heavily contaminated with bowel contents and peritonitis is well established, planned returns to the OR are useful for regular peritoneal washing and prevention of the persistence of infected collections.

**Early Outpatient Care**

The routine length of hospitalization after liver transplantation is approximately three weeks. After discharge the patients are monitored frequently to allow the clinician to recognize the early signs and symptoms of rejection and infection. After the first month to six weeks, follow-up is weekly and then ultimately monthly.

### Table 2. Recommended immunization schedule for liver transplant recipients

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Month 7, Month 9, Month 12</td>
</tr>
<tr>
<td>DTP</td>
<td>Resume standard schedule</td>
</tr>
<tr>
<td>H. influenza type b</td>
<td>Resume standard schedule</td>
</tr>
<tr>
<td>Polio</td>
<td>Resume standard schedule</td>
</tr>
<tr>
<td>Measles, Mumps, Rubella</td>
<td>Month 7 if not previously protected,</td>
</tr>
<tr>
<td>Varicella</td>
<td>Month 7 if not previously protected,</td>
</tr>
<tr>
<td>Pneumovax</td>
<td>Required for patients with splenectomy or</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Newly recommended vaccine for immunocompromised</td>
</tr>
<tr>
<td>Influenza</td>
<td>Yearly</td>
</tr>
</tbody>
</table>

* Inactivated Polio Vaccine
** Patients may experience low grade fever and vesicles at injection site.
*** Penicillin prophylaxis is also recommended for these patients.
LONG-TERM FUNCTION, OUTCOME, GROWTH AND DEVELOPMENTAL RESULTS, FOLLOW-UP AND REHABILITATION

Following the first year after transplant, laboratories are obtained quarterly and children are examined twice yearly to monitor growth and look for signs of chronic graft dysfunction. Cyclosporine and tacrolimus doses are weaned to approximately 50% of the initial values after the first year following transplant. At 18 months after transplant most children can be switched to alternate day steroids. Children receiving primary therapy with tacrolimus may tolerate steroid withdrawal six months after transplant. Unfortunately, it is nearly impossible to predict which children will tolerate complete withdrawal of all immunosuppression. We have treated children who were taken off all immunosuppression for serious complications who did not develop graft rejection, even in long-term follow-up. These children are a minority. Once the immunosuppressive regimen has been decreased somewhat, children can resume a routine schedule of immunizations, see Table 2. The intramuscular polio vaccine preparation should be substituted for the live attenuated vaccine. The approach to immunization with measles vaccine and varicella vaccine can be more liberal. Even though a poor response rate to these two vaccines has been noted in this population, serious consequences of immunization even in children on standard levels of immunosuppression have not been reported. In addition, most liver transplant recipients receive hepatitis B vaccine and yearly influenza vaccine as determined by their local physician. Obviously, children who have a history of asplenia or splenectomy are also immunized with Pneumovax.

One of the most important aspects of long-term follow-up care is monitoring growth and development. Poor linear growth is not uncommon in the first six months after transplant. The onset of catch-up growth is usually between 6 and 24 months after the transplant and can be improved with early withdrawal of corticosteroids. Developmental delay is common in infants in the first year following liver transplant, but steadily improves as children reach school age. Most pediatric liver transplant recipients do have normal school performance once they have rehabilitated from the transplant.

Outpatient management also focuses on patient education, and monitoring compliance. Addressing patient concerns about the cosmetic side-affects of their medication are important issues as well. The final objective of the outpatient visit is to evaluate chronic medical disabilities secondary to the transplant. Most children have minimal medical complaints. A few children are plagued with chronic minor infections. Occasionally, persistence of these infections will warrant a decrease in their immunosuppression to clear the pathogen naturally.

OVERALL RESULTS

The results of liver transplantation in children have steadily improved over the last decade. In recent results, 1 and 5 year survival for children with chronic liver disease exceeds 90%. Transplantation in the setting of fulminant failure is excellent before the onset of severe neurological complications or the progressive failure of other organs such as the kidneys and lungs.
The goal of transplantation is to restore children with liver disease to normal life. Improved immunosuppression and more accurate techniques for the early detection of viral diseases have helped to make this goal an achievable reality.

Organ availability remains one of the largest stumbling blocks on the road to timely transplantation. It is hoped that techniques such as split liver transplantation and living donation in the acute setting, if used on a more regular basis, may substantially reduce waiting times and waiting list mortality for children in need of a liver transplant.

REFERENCES

Intestinal Transplantation

HISTORY

Transplantation of vascularized organs such as the intestine was first conceptualized by Alexis Carrel at the turn of the century, who recognized the potential for such procedures with the establishment of a reliable method of performing vascular anastomoses. However, the feasibility of intestinal transplantation was not demonstrated until 1959 when Richard Lillihei, at the University of Minnesota, reported success in a canine model. This inspired the first human intestinal transplants, which were performed by Ralph Deterling in Boston in 1964 (unpublished). The first reported human intestinal transplant was performed by Lillihei in 1967, and included the entire small bowel and right colon, with the superior mesenteric vessels being anastomosed to the left common iliac vessels. Unfortunately, these and other early attempts which followed were uniformly unsuccessful.

When the effectiveness of cyclosporine was established in other organ transplants in the early 1980s, there was renewed interest in intestinal transplantation. Although the first intestinal transplant using cyclosporine, performed in 1985 by Zane Cohen in Toronto was also unsuccessful, in 1988 Deltz in Kiel, Germany performed what is considered to be the first successful intestinal transplant. The recipient of this living-related allograft remained TPN-free for 4 years before the graft was lost to chronic rejection. Soon after, other successful outcomes were reported by the groups headed by Goulet in Paris, and Grant in London, Canada who had established the first intestinal transplant programs. The successes of these groups inspired other institutions to establish similar programs in the early 1990s.

There are now over 50 centers worldwide which have performed intestinal transplants, with close to 700 transplants performed to date.

INDICATIONS

The indication for intestinal transplant is intestinal failure. This is defined as an inability to maintain greater than 75% of essential nutrition through the enteric delivery of nutrients, and is commonly the result of previous extensive small bowel resections, although severe malabsorption or dysmotility syndromes can also produce this situation. The short bowel syndrome, which manifests in these individuals, consists of massive diarrhea or stomal output, electrolyte abnormalities, fat malabsorption, gastric hypersecretion, vitamin D deficiency, cholestasis, and hepatic steatosis. While in the past patients with intestinal failure would not survive, these patients can now be kept alive with parenteral nutrition. Over the long term parenteral nutritional support can be provided at home, and many individuals with intestinal failure can be maintained with nutritionally adequate diets.

References:
failure have done very well for many years with home parenteral nutrition (HPN). However, HPN is a very expensive therapy, costing $250 to $500 US dollars a day. Furthermore, HPN can be associated with potentially life-threatening complications such as catheter-related sepsis, catheter-related thrombosis, metabolic derangements, liver dysfunction, and bone disorders. In the pediatric population and in adults with extremely short guts (i.e., < 50 cm with colon, < 100 cm without colon), gross impairment in liver function is seen in up to 50% of patients. Because central venous access is required for administration of TPN, and recurrent central line placements often lead to venous stenosis or occlusion, long term HPN often results in a loss of sites for vascular access. 

Since in some patients HPN may only be needed temporarily, before considering intestinal transplantation attempts at establishing enteral feeding should be pursued since there can be significant adaptation in intestinal function. Adaptation of the intestine is a result of both an increased absorptive surface due to hypertrophy and an increase in the efficiency of absorption. Generally, if an individual with intestinal failure remains HPN-dependent after 1 year, intestinal transplantation should be considered. If life-threatening complications of HPN develop prior to 1 year, intestinal transplantation should be considered earlier. If during the intestinal transplant assessment evidence of irreversible liver disease [cirrhosis, fibrosis, portal hypertension] is discovered, a liver/intestine transplant should be performed. If the underlying disease process compromises the organs supplied by both the mesenteric and celiac arterial systems, or if it mandates replacement of other sections of the alimentary tract, a multivisceral transplant (i.e., stomach, duodenum, pancreas, liver, small intestine, and colon) should be considered.

Although no specific disease entity, in and of itself, is an indication for intestinal transplant, in the intestinal transplants performed to date the primary diseases which have most commonly led to consideration of an intestinal transplant are, in adults: mesenteric thrombosis, Crohn's disease, trauma, volvulus, desmoid tumor, Gardner's syndrome/familial polyposis; and in children: volvulus, gastroschisis, necrotizing enterocolitis, pseudo-obstruction, intestinal astresia, and Hirschsprung's disease. 

**CONTRAINDICATIONS**

In general, intestinal transplants should not be performed in individuals who have significant co-existent medical conditions that have no potential for improvement following transplantation, and which would negate any potential benefit provided by an intestinal transplant in terms of life expectancy or quality of life. If the patient has active infection, malignancy, or HIV, transplantation is contraindicated. If there is substantial evidence to indicate that a potential recipient or the primary care givers are not willing or able to reliably assume the responsibilities of the day-to-day management of the potential recipient following the transplant, transplantation is contraindicated.
PRETRANSPLANT RECIPIENT EVALUATION

All individuals under consideration for intestinal transplant should be seen and evaluated by a multidisciplinary intestinal failure team including transplant surgery, gastroenterology, nutritional services, psychiatry, social work, anesthesia, and financial services. Further consultation with other specialties [i.e., cardiology, hematology, chest medicine, infectious disease, chemical dependency, dentistry, etc], will be required in some cases. Baseline laboratory investigations including routine blood work, ABO blood group determination, HLA status, and panel reactive antibody status will be performed. If not done previously, the GI tract should be assessed both radiologically and endoscopically to accurately determine the length and condition of the remaining bowel. It is also important to establish which large veins are available for vascular access, as many of the patients will have limited options. Living related donor transplantation can be discussed as an option if a potential living related donor is available.[14]

If after these evaluations there is consensus that the patient is a good candidate for intestinal transplantation, the patient will be listed. While waiting for a donor to become available the stable patient should be reassessed every three months to determine whether there is any change in their PRA status, deterioration in liver function, or development of other medical problems. Furthermore while waiting for intestine only transplantation, the HPN administration should be monitored very closely to ensure that it does not contribute further to the development of hepatic steatosis and fibrosis since optimal balancing of carbohydrates and lipids in the HPN solutions can minimize the development of hepatic pathology. These patients will also need ongoing maintenance of their central lines to minimize line-related complications such as infections and thrombosis. Furthermore while waiting for transplantation close attention must be paid to fluid and electrolyte disturbances which are common due to the often-excessive output from the residual GI tract, particularly in individuals who continue to eat or drink. In some instances patients who have dysfunctional intestine [i.e., dysmotility or malabsorption syndromes] or a blind loop, which result in stasis of intestinal contents, will develop severe problems with bacterial overgrowth and translocation resulting in recurrent, bacteremia and life threatening sepsis. Surgical revision to eliminate blind loops including, in extreme situations, total enterectomy of dysfunctional small bowel are sometimes warranted to keep these patients alive until transplantation can be performed.

DONOR EVALUATION AND MANAGEMENT

Cadaveric Donors

All cadaveric donors are potential intestine donors. The cadaveric donor needs to be ABO compatible with the recipient and because of the risk of graft versus host disease ABO identical combinations should be used in most circumstances. In most cases, extensive prior bowel resection has significantly reduced the size of
the recipient peritoneal cavity and therefore a donor that is 50 to 75% the size of the recipient is needed. In certain circumstances segments of the intestine from a larger donor may be considered.

Donors should have no previous history of significant intestinal pathology. As with all organs donors there should be no significant hemodynamic instability, sepsis, history of malignancy or chronic infection, severe hypoxia, severe acidosis, and they must have negative serology for HIV, hepatitis B and hepatitis C. A cross match should be performed either using a standard cytotoxicity assay or flow cytometry. In certain circumstances, if the cross match results are not available, but the patient has had no evidence of presensitization based on pre-transplant serologic surveillance, it may be reasonable to proceed without the cross match results. Because of the need to minimize the intestinal cold ischemia time (< 6 hours), it may not always be possible to obtain the cross match results in time. Although HLA matching has not been studied extensively in small bowel transplantation it is also useful to know the HLA status of both donor and recipient, particularly if the recipient in known to be sensitized to certain HLA antigens.

Two other important considerations are the CMV and EBV serologic status of the donors and recipients. Transplantation of a serologically positive donor into a serologically negative recipient for either of these viruses can have serious consequences. In addition to the risk of a systemic CMV infection, a CMV enteritis can occur which can lead to graft loss. A new EBV infection combined with posttransplant immunosuppression puts the patient at high risk for developing a post transplant lymphoproliferative disorder (PTLD).

If a donor is considered suitable, an NG tube should be placed and oral antibiotics administered to try and decrease bacterial counts in the donor gut. Amphotericin B, Neomycin, and Erythromycin base are typically administered immediately after the decision is made to go ahead with the procurement and then again at initiation of the multi organ procurement. A formal bowel prep should not be performed in most circumstances because, with the time constraints involved, the bowel will end up severely distended making it difficult to transplant. In the rare circumstance that there will be 12 to 24 hours between the identification of a donor and the donor procurement, a formal bowel prep may be considered. Some programs also consider administering OKT3 to the donor to decrease the numbers of lymphocytes in the allograft prior to transplantation, although the merit of this has not yet been determined.

Because the optimal cold ischemia time for intestinal grafts is less than 6 hours, careful attention must be given to the timing of the donor and recipient procedures to prevent prolonged cold ischemia. Consideration should also be given to what other organs are going to be procured, as this may influence the length of the donor procedure and the approach used by the small bowel procurement team.

**LIVING DONORS**

If a living donor is being evaluated, it is important that the potential donor be evaluated by a multidisciplinary team that includes transplantation surgery, GI medicine, psychiatry, nutritional services, and social work. To avoid a conflict of
Intestinal Transplantation

interest, it is imperative that the physician who is in charge of working up the donor not be an active part of the transplant team. As with any living donor procedure, the potential complications should be explained in great detail to the prospective donor on multiple occasions. It should also be made quite clear to the patient that other options besides using a living donor are available. Time must also be taken to fully understand the nature of the relationship between the donor and the recipient. Living donation should not be pursued if coercion or financial incentive appear to be the primary motivation for donation.

If a number of potential living donors are available, particularly among family members, then careful consideration should be given to the best available HLA match. The donor-recipient size discrepancy must also be considered but since, in a living donor, only a segment of the intestine is transplanted, size limits are less restrictive. As with cadaver donors, the donor and recipient should be ABO identical, although in some circumstances ABO compatible combinations can be considered.

As with cadaveric donors, living donors must be free of significant pathology involving the GI tract. Any potential living donor must be in good health with no previous significant medical problems, including diabetes, malignancy, or chronic infection. There should be no history of substance abuse or other high-risk activities in the donor, and no significant psychiatric history. Serology in the living donor must also be negative for HIV, Hep C and Hep B. Obese donors should be avoided. As with cadaveric donors, the CMV and EBV status of the donor and recipient must be carefully considered and the combination of positive donors to negative recipients should be avoided. The living donor should be worked up completely including CBC, electrolytes, liver function tests, EKG, chest x-ray. The GI tract should be evaluated endoscopically and if any concerns exist, GI contrast studies should be performed. A mesenteric angiogram with selective study of the SMA and its venous phase should be performed to ensure that the terminal SMA and SMV are adequate.

One day prior to surgery the potential donor should be kept on clear fluids and administered neomycin 1 gram and erythromycin base 1 gram PO at 1300 and 1400 and 2300 hours. The potential living donor should also undergo a formal bowel preparation using GoLYTELY (4L) the day prior to surgery.

DONOR PROCUREMENT

It is important for all procurement teams to work closely in coordinating their various roles in the procurement process. The small bowel team must work most closely with those teams that are procuring other intra-abdominal organs. Prior to initiating the procurement there must be an agreement as to where the portal vein, or superior mesenteric vein will be divided. If no pancreas is being procured, then the portal vein is usually divided at least 2 centimeters superior to the splenic vein take off. If the pancreas is going to be used then the superior mesenteric vein must be taken immediately below the uncinate process. With regards to the artery, if the pancreas is not being used then typically the entire superior mesenteric artery will be taken along with a long tube of adjoining aorta extending up into
the chest, to provide additional length for the artery should it be necessary. If this is done, great care must be taken in preserving a small Carrel patch at the origin of the celiac artery for the liver procurement team, if requested. If the pancreas is going to be used then the proximal superior mesenteric artery will need to be preserved for the head of the pancreas and the artery will have to be divided immediately below the uncinate process. In all of these circumstances, extra segments of donor artery, preferably the iliac artery; and donor vein, preferably the iliac vein, should be taken in case vascular extension grafts are needed when the small bowel allograft is revascularized.

In general, after the abdomen is open, the first step in small bowel procurement is to perform a gross visual inspection of the small bowel. If all appears well, the omentum should be taken off the right side of the transverse colon to approximately the mid transverse colon. Care must be taken not to transect the transverse mesocolon. At this point, after identifying the middle colic vessels, a site immediately to the donor’s left of the middle colic vessels is chosen as the distal extent of the small bowel graft. A small hole is made in the transverse mesocolon at this site in preparation for transection of the bowel. Next after entering into the lesser sac along the greater curvature of the stomach near the pylorus, the pylorus is encircled taking care not to injure the arteries going to the liver. An NG tube is then manipulated into the duodenum where the Amphotericin/Neomycin/Erythromycin base solution is infused. Once the solution has been infused [250-500 cc], and the NG tube is withdrawn into the stomach, the pylorus is divided using a GIA stapler. After a few minutes are given for the solution to pass through the small bowel and into the colon, the jejunum just distal to the ligament of Treitz is encircled and divided using a GIA stapler. Next the transverse colon should be divided at the previously selected site. If any solid stool is palpated in the right colon it should be milked distally prior to transection so that it is not included in the graft. Therefore, the intestinal segment to be removed extends from the ligament of Trietz to the mid-transverse colon. After this segment has been completely mobilized, attention is diverted to the arterial and venous supply, which are isolated as described previously.

For procurement of a liver-intestine graft, the portal vein is not divided but is procured in continuity with the liver after ligating all posterolateral branches in the head of the pancreas. The correct orientation of the portal vein should be made apparent using small clips or indelible ink to avoid twisting during implantation. The hepatic arteries are also not divided but are procured in continuity with the celiac artery, SMA and a long, adjoining segment of thoracic aorta.

For a multivisceral transplant, all organs to be transplanted are removed en bloc with their blood supply procured in continuity with the celiac artery, SMA and a long, adjoining segment of thoracic aorta.

When the organs are ready for removal a cannula is placed in the distal aorta, which is flushed retrogradely with University of Wisconsin solution. Simultaneous with initiation of the flush, the supra-hepatic vena cava is partially divided in the chest cavity to facilitate extravasation. The thoracic aorta is also clamped in the chest. After the small bowel graft has been extravasated and completely flushed
Intestinal Transplantation

with cold preservation solution, it is removed and placed in sterile bags which are placed in a cooler for transport.

It is very important that the small bowel procurement is done in close coordination with the preparation of the recipient. The two procedures should be timed so that when the donor team arrives back at the recipient hospital, all is ready for the graft revascularization.

RECIPIENT PROCEDURE

When a donor is first identified the recipient must be notified immediately so that their surgery can be coordinated with the donor procedure. The waiting recipient should at all times be prepared to transport themselves to the hospital within a couple of hours of notification. Preoperative blood work and other mandatory preoperative tests should be obtained immediately upon arrival to the hospital and broad spectrum antibiotics should be administered approximately 15 minutes prior to the opening incision. Since most intestinal transplant recipients have limited vascular access, the current TPN line may be utilized. The surgical team should inform the anesthesia team of potential available sites for other I.V. access, so that futile attempts to establish IV access are avoided.

The recipient is taken to the OR at an appropriate time dictated by the amount of surgery that is anticipated to prepare for implantation of the donor graft. In some circumstances residual segments of diseased bowel will need to be removed from the potential recipient. Furthermore, a decision will have to be made as to which vessels the donor bowel will be anastomosed to. Ideally, if they are not diseased and are of satisfactory caliber, the recipient superior mesenteric artery and vein can be used. Alternative choices would be the infrarenal aorta for arterial input and the portal vein or inferior mesenteric vein for venous drainage. If the portal venous system is not accessible or useable, the inferior vena cava can also be used. Although anastomoses between a donor portal venous branch and the recipient cava are not physiological, in the instances where they have been performed, patients have had no adverse consequences.

For a liver-intestine graft, the caval anastomoses are performed as with a liver-only transplant. The recipient portal vein, which will still be draining the residual recipient visceral organs can either be anastomosed end-to-side to the recipient cava or to the donor portal vein. The aortic segment with its celiac and SMA trunks intact is then anastomosed end to side to the infrarenal aorta.

For a multivisceral graft, if the liver is included, the caval anastomoses are performed followed by the donor aortic segment to recipient infrarenal aortic anastomosis. If the liver is not included, the donor portal vein is anastomosed to the recipient portal vein or cava. In addition to preparing sites for the vascular anastomoses, appropriate sites for the proximal and distal intestinal anastomoses should also be identified. Ideally, the proximal end of the donor intestine will be anastomosed to the most distal and accessible segment of the recipient’s remaining small intestine, which typically is at or distal to the ligament of Treitz. If in the pretransplant evaluation the recipient has been shown to have severe gastric dysmotility with delayed gastric emptying, consideration of what to do with the stomach must be included in
the overall surgical plan. The management of the stomach in these circumstances is somewhat controversial. The options include:

a. Doing nothing at the time of transplant and following the patient to see if gastric emptying remains a problem post transplant.

b. Performing a gastrojejunostomy—anastomosing proximal donor intestine to the stomach.

c. Performing a partial gastrectomy and gastrojejunostomy.

d. Performing a multivisceral transplant which would include stomach, duodenum, pancreas, intestine and, if necessary, liver.

Another area of controversy is whether a segment of colon should be transplanted with the small intestine or not. The primary advantage of transplanting the colon is that it helps to control the severe fluid and electrolyte imbalances which can occur posttransplant. The disadvantage is that it may predispose to a higher incidence of bacterial translocation and infectious complications.21

If the recipient has remaining healthy colon, its proximal end would be the ideal site for anastomosis to the distal end of the donor intestine. If the recipient has had a proctocolectomy, the distal end of the donor intestine can be brought out as an end colostomy or ileostomy. In certain circumstances it may be preferable to perform a pelvic pull-through with a colo-anal anastomosis, but this is often better left for a second operation. If an end-ileostomy is not created, a site for a loop ileostomy must be selected. An ileostomy of some form is essential to provide direct vision and direct endoscopic access to the small bowel for surveillance following the transplant. Some centers perform a Bishop-Koop type of ileostomy rather than a loop ileostomy.

Another important consideration in the recipient operation is the placement of a feeding jejunostomy tube. Because early establishment of enteral feeding is essential, and since the establishment of oral feeding is less predictable a feeding jejunostomy should be placed at the time of transplant. The safest approach is often to put a percutaneous gastrojejunal tube into the native stomach, passing it into the proximal jejunum of the intestinal allograft. This precludes any allograft-related problems compromising the integrity of the tube insertion site. In some circumstances, however, it may be preferable to place a jejunostomy tube directly into the donor jejunum.

Upon arrival of the donor team at the recipient hospital, implantation of the graft must begin as soon as possible. The patient should be fully heparinized prior to the vascular anastomosis. Overall the total cold and warm ischemia time should be kept less than 6 hours. The warm ischemia time should ideally be less than 30 minutes. After completion of the vascular anastomoses and reperfusion of the graft, if all segments are perfused well the proximal and distal intestinal anastomoses should be performed followed by the ileostomy. The patient can then be closed after the feeding jejunostomy is placed. The recipient should be left with a tube or combination of tubes that will both decompress the stomach and allow feeding in the jejunum.
POSTOPERATIVE MANAGEMENT

The recipient should be established on immunosuppression immediately following surgery. For the first several days posttransplant, only select medications, including Tacrolimus should be administered via the GI tract. In circumstances where Tacrolimus absorption via the GI tract has been questionable, sublingual administration can be utilized. In most circumstances Tacrolimus is the main immunosuppressive drug. However, if the patient is intolerant of Prograf, consideration can be given to other immunosuppressive regimens based on Neoral. Sirolimus, especially in combination with Tacrolimus, has improved patient and graft survival and is now being incorporated into most immunosuppressive protocols. Steroids are also included in the postoperative immunosuppressive regimen. While induction with OKT3 or ATGAM has generally been avoided because of the higher incidence of PTLD associated with intestinal transplantation, some centers have been reevaluating their role. Alemtuzumab (CAMPATH-1H), an anti-CD52 mAB, has also been used by some centers although its safety and efficacy in intestinal transplantation has not yet been clearly established. Monoclonal anti-IL2 receptor antibodies (Basiliximab, Daclizumab) are currently being used for most intestinal transplants, as they appear to provide benefit. While some programs have included mycophenolate mofetil, others have avoided it because of its association with gastrointestinal side effects. Prostaglandin E1 is commonly administered intravenously while the patient is in the hospital, both for its ability to improve the small bowel microcirculation and its potential immunosuppressive effects. Broad-spectrum intravenous antibiotics are usually continued for at least 1 week following the transplant.

It is imperative to maintain prophylaxis for cytomegalovirus (CMV) and Epstein Barr virus (EBV) infections postoperatively particularly where the donor is positive for CMV or EBV and the recipient is negative. CMV prophylaxis is best accomplished with Gancyclovir, although CMV immune globulin (Cytogam) has also been used. Acyclovir, which is less effective than Gancyclovir for CMV, is effective prophylaxis for EBV. Intravenous immune globulin (IVIG) is also used by some centers as EBV prophylaxis.

In the immediate postoperative period it is essential to check hemoglobins regularly for evidence of bleeding. It is also important to monitor serum pH and lactate levels to detect any evidence of intestinal ischemia or injury. Prograf levels should be followed daily and doses adjusted to achieve a serum level of 20-25 ng/ml in the early posttransplant period.

Approximately 5 days post transplant, if all is stable, an upper GI contrast study should be performed to ensure that there is no leakage or other gross abnormality in the newly established gastrointestinal tract. If the upper GI contrast study reveals no contraindication, tube feed should be initiated slowly but can usually be advanced to provide full nutritional support within a couple of days. The ideal features of an enteral feeding solution to be established in a new intestinal transplant recipient are that it: (a) provides maximum calories with minimal volume without being hyperosmolar; (b) has minimal or no complex fatty acids [medium chain triglycerides are ok]; and (c) is supplemented with glutamine and/or arginine.
Postoperative Surveillance

In the postoperative period, several potential complications need to be closely watched for, including the following.

Rejection

Acute cellular allograft rejection is unlikely to occur within the first few weeks following the transplant, provided immunosuppression is adequate. Subsequently, rejection can occur at any time but is most common in the first year, particularly the first 6 months. Unfortunately, as of yet, there is no single blood test, which will detect an early rejection. Therefore, suspicion of rejection must be based on clinical evaluation. Although no single sign, or combination of clinical signs is entirely reliable, in most instances rejection is associated with fever, a significant increase in stomal output, and GI symptoms such as abdominal pain, cramping, nausea, vomiting and diarrhea.

Although most lab tests are not helpful in confirming the diagnosis, chromium EDTA, or Technetium DPTA isotope studies have been useful in identifying increased intestinal permeability which correlates well with, but is not specific for, rejection. If rejection is suspected, endoscopic evaluation of the intestinal graft must be performed. The endoscopic evaluation should include as much of the small bowel as possible and biopsies from numerous sites (at least 6) should be obtained, since rejection can often be segmental. The loop ileostomy greatly facilitates this type of assessment and for that reason the ileostomy is usually kept in place for 6 months to a year following the transplant. Although the endoscopic appearance of rejecting small bowel is often abnormal with evidence of inflammation and ulceration, in early rejection it can be quite normal. Zoom-endoscopy appears to provide more a valuable endoscopic identification of acute rejection in the small bowel. The gold standard for diagnosing rejection is histologic evaluation of the biopsies. Typically early rejection is associated with increased apoptotic figures [normal less than 2 to 3 per high power field]. Other histologic findings associated with rejection include: the presence of activated lymphocytes in the lamina propria; loss of goblet cells; loss of villus height, and ulceration.

When a diagnosis of rejection is made, the patient should be treated with Solumedrol 500mg IV for 3 days. Prograf levels should be rechecked and doses increased accordingly. If there is persistent evidence of rejection following treatment with steroids, the patient should be treated with OKT3 or Thymoglobulin. If, despite maintaining adequate immunosuppressive levels, rejection episodes continue to occur, consideration should be given to adding additional drugs, such as Sirolimus to the immunosuppressive regimen. Because escalation of immunosuppression can be complicated by life threatening infections or malignancies, such patients should be carefully monitored.

Infection

Patients who undergo small bowel transplant are even more susceptible to infectious complications than other transplant recipients. There are primarily two reasons for this:
1. The intestinal allograft is transplanted with a significantly higher load of microorganism than any other organ allograft. Therefore, any process which compromises the intestinal allograft will influence the containment of these microorganisms within the graft and contribute to their spread to various areas of the body.

2. Because intestinal rejection is difficult to detect and because severe rejection can often lead to life threatening sepsis, these patients are maintained on higher degrees of baseline immunosuppression than recipients of other organ transplants.

**Bacterial Infections**

When bacteria translocate from the compromised intestinal allograft, there are commonly two places where they go initially. Since the lymphatics are divided in the procurement of the intestinal allograft it is common that there is leakage of intestinal lymph into the peritoneal cavity. This often contains bacteria. While typically the peritoneal cavity is capable of handling a moderate load of bacteria, in the immunocompromized state—particularly when significant ascites is present—bacterial peritonitis can occur. The second route by which bacteria can spread is by direct translocation into the portal circulation and subsequent dissemination to other sites. Particularly common infections resulting from bacterial translocation are central line infections and pneumonias. The typical organisms are consistent with those, which are found in the GI tract and include E.Coli, klebsiella, enterobacter, staphylococci enterococci, etc. Because of the degree of immunosuppression used, other typical and atypical postoperative infections are more likely to occur.

**Viral Infections**

A primary concern with intestinal transplantation is the development of a CMV infection, which can manifest as CMV enteritis that can be severe and lead to graft loss. In general, transplantation of a graft from a CMV positive donor to a CMV negative recipient is avoided. The clinical manifestations of CMV enteritis are not unlike that of rejection with fever, increased stomal output and GI symptoms. Other important clues which may sway the clinical diagnosis more towards CMV enteritis include: the CMV status of the donor and recipient, the degree of immunosuppression at the time symptoms developed, and a positive CMV antigenemia assay. Also with CMV infections there is typically a decrease in the white blood cell count and flu-like symptoms. Endoscopy should be performed and multiple biopsies taken if there is a clinical enteritis. While the histologic picture of CMV can sometimes be similar to that of rejection, with CMV enteritis the presence of CMV inclusion bodies is diagnostic. If CMV is diagnosed, the patient should be treated with therapeutic doses of Gancyclovir. If there is evidence of Gancyclovir resistance, Foscarnet or CMV immune globulin (Cytogam) should be considered. Furthermore, immunosuppression should be reduced until the CMV infection is controlled.
Epstein Barr virus (EBV) associated infection can initiate an entire spectrum of disease. Those particularly at risk are recipients who are EBV negative and who receive an EBV positive graft. An acute EBV virus infection is typically associated with severe malaise and fever and flu-like symptoms i.e., infectious mononucleosis. Other evidence of EBV infection can include an increase of liver function tests, splenomegaly and lymphadenopathy. In certain instances an EBV infection can progress to a post transplant lymphoproliferative disorder (PTLD) which can develop into a malignant lymphoma. Surveillance for PTLD should therefore began immediately following the transplant particularly in EBV negative recipients who have received EBV positive grafts. PCR has been utilized to semiquantitatively monitor EBV replication by quantitatively determining the amount of EBV encoded RNA (EBER) in the serum as an early warning of an impending PTLD. Other approaches using in situ hybridization have also been described.

While there is no standardized strategy for preventing PTLD, two basic approaches have evolved. One approach is to give long term prophylaxis with recipients maintained on ganciclovir and/or IVIG for 3 to 12 months following the transplant. The other approach is to have a shorter period of prophylaxis (2 to 6 weeks), followed by surveillance as described above and preemptive therapy should surveillance identify increased EBV replication. Similar strategies are also used or CMV surveillance.

POSTTRANSPLANT FUNCTION

Typically the transplanted intestine will initiate peristalsis immediately after reperfusion. However, in the process of procuring the donor intestine all extrinsic innervation to the bowel is disrupted. This and other factors contribute to a less orderly peristalsis than is seen in a normal intestine. Often a more significant problem is the dysfunction of residual native intestine in a patient with a primary dysmotility syndrome. In some instances the stomach, duodenum, and colon, etc, will be left in place to best approximate re-establishment of normal gastrointestinal continuity. Sometimes these retained native segments function adequately while in other instances they do not. It remains controversial whether such patients are best served by isolated intestinal transplants, or by multivisceral transplants which would provide a new stomach, duodenum and colon if necessary.

The absorptive capacity of the transplanted intestine is typically good. While there may be some initial malabsorption of carbohydrates, for the most part carbohydrate absorption appears to normalize within the first several months as determined by d-xylose absorption. Clearly, absorption of immunosuppressive drugs, particularly Prograf, is instantaneous and some transplant programs initiate oral immunosuppressive drugs immediately following surgery. While drug malabsorption has been described, difficulty in obtaining levels is often associated with inability to retain ingested drugs because of nausea or vomiting, or noncompliance. Although very little has been done to measure amino acid absorption in intestinal transplantation, this also appears to be adequate quite early as determined by nonspecific markers of protein nutrition such as pre-albumin. Fat absorption on the other hand is impaired for several months following intestinal transplantation. Because the intestinal lymphatics are unavoidably disrupted in
the procurement process, intestinal lymphatic drainage is not re-established for several months following the transplant. Absorption of dietary lipids, which primarily are made up of long chain triglycerides, depends on lymphatic drainage. Medium chain triglycerides (MCTs), i.e., those consisting of 8 to 12 carbon fatty acids, can be absorbed directly into the portal circulation. For these reasons it is essential to supplement enteral feeds with MCTs for several months following transplantation. Use of more complex fatty acids will lead to malabsorption of fat with increased ileostomy output and possible dehydration. To avoid an essential fatty acid deficiency, it may be necessary to intermittently supplement with intravenous fats, until the intestinal lymphatics are reestablished. Because of the obligatory fat malabsorption, there can also be malabsorption of the fat-soluble vitamins [Vitamin D, E, A, K]. Despite this, 72% of adults and 93% of children gain weight, and essentially all achieve their ideal body weight range.31

Because of the abnormal intestinal motility and malabsorption, associated with the early posttransplant period, the ileostomy output can be unpredictable and often excessive. Even in the best of circumstances, high ileostomy output can be anticipated early once full enteral nutrition has been established. Very close attention must be made to the overall fluid and electrolyte balance to prevent severe dehydration and/or electrolyte imbalances. It is imperative, in addition to accurate monitoring of daily in and outs, to follow daily weights and electrolytes. Once enteral nutrition is found to be providing all nutritional requirements, TPN is discontinued. If weight is maintained or weight gain occurs, and there is no significant evidence for protein malnutrition, TPN can be permanently discontinued. After a brief period of adjustment, ostomy output should become quite predictable over a given period of time. Dramatic changes in ostomy output should be investigated, as this can be an early indicator of rejection or other pathology. Overall, 70-80% of patients who undergo successful transplantation can be completely removed from TPN.32

PATIENT AND GRAFT SURVIVAL

The one-year graft survival for intestinal transplants performed since 1991 is approximately 60%. Despite early trends, there appears to be no difference in long-term graft survival when other organs are transplanted with the intestine. With regards to patient survival, overall 1-year survival for intestine-only transplants has been approximately 70%, while for intestine plus liver, or multi visceral transplants 1-year patient survivals have been 62% and 52%, respectively. However, evaluation of the most recent cohort of transplants performed at the most experienced centers suggests that patient survival in two of these three groups is improving with 77%, 69% and 62% one year patient survivals in intestine-only, multivisceral, and intestine plus liver transplants respectively. While meaningful data on long term graft and patient survival is not yet available, it appears that a plateau in survival may begin to occur at approximately the two-year mark. As has been the case with all newly established organ transplants, there appears to be learning curve phenomena with improved patient survivals observed in the most experienced centers.32
MORBIDITY

Acute rejection has occurred in 79% of patients undergoing intestine-only transplants. Once again the liver, and perhaps other organs, may have a protective effect since the acute rejection rates for liver/intestine and multivisceral transplants have been 71% and 56% respectively. Similarly, chronic rejection, which has been demonstrated in 13% of intestine-only transplants, has been uncommon in liver/intestine (3%) and multivisceral transplants (0%). Despite the fact that most centers avoid transplanting intestinal grafts from cytomegalovirus (CMV) positive donors, CMV infections occurred in 24% of intestine-only grafts, 18% of liver/intestine grafts, and 40% of multivisceral grafts.

Post-transplant lymphoproliferative disorders (PTLDs) have been seen in 8.3% of intestine-only, 13.3% of liver/intestine, and 15.8% of multivisceral grafts. PTLDs often manifest as fever and lymphadenopathy or lymphoproliferation in either donor or recipient tissue. Lymphoma can also manifest with gastrointestinal symptoms including nausea, vomiting, diarrhea, bowel obstruction, GI bleeding, or perforation.

The incidence of PTLD in intestinal transplant recipients is higher than in other organ transplant recipients. The occurrence of PTLD clearly correlates with the intensity of immunosuppression. Significant increases in the incidence of PTLD are noted in patients who receive OKT3 or ATGAM, especially if their total antibody course exceeds 21 days. While PTLD tends to first manifest between 2 weeks and 6 months after a transplant, it can appear at any time.

The diagnosis of PTLD usually requires a biopsy. Often this is most easily obtained from an enlarged superficial lymph node or from clinically or radiologically involved tissue. If the suspected organ is the intestine graft itself, it can sometimes be difficult to differentiate PTLD from rejection, or CMV infection. When this is the case it is often useful to obtain further studies including EBER staining of suspicious tissue. It is often also useful to evaluate the serum for a typical monoclonal or polyclonal immunoglobulin bands which can sometimes be present. Gene studies are often helpful to identify abnormal karyotypes which can aid in diagnosis and prognosis (C-myc, N-ras, p 53) is polyclonal or monoclonal. It should also be determined whether the abnormal lymphocytes sites are primarily B cells or T cells. T cell lymphomas are less common than B cell lymphomas in post-transplant PTLDs.

If the diagnosis of PTLD is made, immunosuppression should be reduced to approximately half of what it had been. In approximately one third of cases, this will result in a remission of the PTLD. Anti B-cell mAb (Rituximab) therapy is initiated. If after 2 weeks there is no evidence of improvements, all immunosuppression should be discontinued and serious consideration should be given to additional therapeutic measures including chemotherapy and/or adoptive immunotherapy. If necessary, an intestine-only graft can also be removed.
MORTALITY

Overall, the most significant cause of morbidity and mortality has been infectious complications. Over half (51%) of the deaths in intestinal transplant patients have been clearly attributed to sepsis. Other causes of death have included rejection (10%), technical complications (7%), PTLD/Lymphoma (7%), and respiratory causes (7%).

FUTURE DIRECTIONS

Intestinal transplantation provides unique and difficult challenges. Because of the delicate balance that must be maintained to provide adequate immunosuppression without over immunosuppression, it is imperative that a simple marker be developed which will alert clinicians that an early rejection is brewing. Another goal is to develop strategies, which eliminate or minimize the risk of rejection. To this end many researchers are attempting to develop strategies for inducing tolerance. Several groups have attempted to induce a state of microchimerism and tolerance by transplanting bone marrow along with the intestinal allograft. To date, this approach has not been shown to be effective. Other groups have administered donor specific transfusions simultaneous with implantation of the intestinal graft. While there are some preliminary animal studies suggesting that this approach might be effective, its benefit has not yet been proven in humans. Another approach, which has been effective in kidney transplantation, is HLA matching. Although due to time constraints this may not always be practical in the realm of cadaveric intestinal transplantation, it is possible with living related donors. While the experience with living related donor intestinal transplantation has been very limited to date, some of the longest surviving intestinal grafts from the pre cyclosporine era were achieved when living related donors were utilized. More recent experiences with modern immunosuppression have shown that graft survival with living donors is at least comparable to that achieved with cadaveric donors. The potential advantages of using living donors are: (a) opportunity for better HLA matching; and (b) better control over ischemia times. The potential disadvantages are that: (a) the donor, who does not need a surgical procedure, is put at risk; (b) the allograft will consist of a shorter segment of bowel with smaller blood vessels.

SUMMARY

Intestinal transplantation is an option for individuals who are otherwise committed to a life of HPN because of intestinal failure. Intestinal transplantation is a fairly new procedure, which is still evolving, and at this time is still associated with significant risks. Rejection in intestinal transplantation is controllable with current immunosuppressive drugs, provided it is identified early. Infectious complications are the most significant cause of morbidity and mortality with intestinal transplantation. Post transplant lymphoproliferative disorders are also more common after intestinal transplantation, particularity when multivisceral transplants are performed. New strategies for detecting rejection and preventing infection are needed for intestinal transplantation to achieve the level of success that has been achieved with other solid organ transplants.
REFERENCES

Anesthesia for Organ Transplantation

Andre DeWolf, Yoogoo Kang and Laurence Sherman

After the major advances in effective immunosuppression and organ preservation in the early 1980s, there was an exponential increase in the number of transplant procedures and transplant centers. Anesthesiologists had to learn quickly how to care for these patients with organ failure and allow these complex procedures to be performed without further insults to other organs of the recipient. After these hectic years, organ transplants became more common procedures in these institutions, with anesthesiologists better prepared. Thus, after the initial development of anesthetic protocols, we have seen more delicate refinements in these anesthetic techniques. Anesthetic improvements are based on better understanding of the pathophysiology of organ failure and surgical procedures, but success can only be attained by paying attention to countless details. This chapter summarizes the anesthetic management for liver, heart, lung, kidney, and pancreas transplantation.

LIVER TRANSPLANTATION

Providing anesthetic care to a patient undergoing liver transplantation is one of the most challenging tasks for an anesthesiologist. Liver transplantation is a complex and formidable procedure, frequently involving major hemodynamic changes due to preload and afterload changes, massive blood loss, coagulation changes, acid-base changes, and electrolyte changes (hyperkalemia, hypocalcemia) of magnitudes that are unseen in any other procedure. Furthermore, patients with severe liver disease may have significant dysfunction of several other organ systems. Proper management starts with an appropriate and complete preoperative work-up; however, the issues that are of significant importance for the anesthetic management of patients undergoing liver transplantation will be discussed here.

PREOPERATIVE EVALUATION

In patients with acute or subacute liver failure requiring urgent transplantation there is little time to do an extensive preoperative evaluation. Most patients however have to wait a significant amount of time for their transplant, and therefore evaluation should be complete. Anesthesiologists should be part of the multidisciplinary team determining appropriate candidacy for transplantation for patients with severe liver disease.

Cardiovascular System

Patients with severe liver disease have a hyperdynamic circulation, with a high cardiac output and a low systemic vascular resistance. The systemic vasodilation
is reflected by dilated capillaries and peripheral arteriovenous shunting, probably
the result of abnormal nitric oxide and endothelin metabolism, although other
factors may also play a role. The high cardiac output is achieved by an increase in
both resting heart rate and stroke volume, and leads to an increased mixed venous
oxygen concentration. Echocardiography typically shows mild four-chamber
enlargement; this should not be interpreted as congestive heart failure. Similarly,
because of the systemic vasodilation, mild hypotension (systolic blood pressure
90-100 mm Hg) is frequently seen, and again is not necessarily an indication of
left ventricular dysfunction.

Coronary artery disease (CAD) should be excluded in patients with risk factors
(diabetes mellitus, positive family history). In patients with limited mobility due
to severe ascites or encephalopathy, dobutamine stress echocardiography may be
the preferred initial preoperative test. Whether CAD is treated surgically or medi-
cally, liver transplantation in these patients carries an increased perioperative mort-
ality rate (approximately 31%) with a 3-year mortality rate of 50%. This high
mortality rate has to be considered when the decision is made to accept a patient
with CAD for liver transplantation. Echocardiography has the additional advantage
that overall cardiac function can be assessed and other problems can be diagnosed
(pericardial effusion, valvular disease). Overall, patients with cardiac dysfunction
may not tolerate the intraoperative hemodynamic changes. In addition, the increase
in systemic vascular resistance after successful transplantation represents an increase
in afterload for the left ventricle, and may lead to overt cardiac failure. Abnormal
cardiac function may be seen in patients with hemochromatosis and alcoholic liver
disease, and while this may not be apparent preoperatively at rest, a dobutamine
stress echocardiography may elicit reduced cardiac reserve. Other appropriate tests
in selected patients include stress electrocardiography, resting echocardiography,
or stress echocardiography; cardiac catheterization may be necessary to make the
final diagnosis.

Pulmonary hypertension is seen more frequently in patients with portal
hypertension than in the general population for unknown reasons. Because of
high perioperative mortality, liver transplantation is probably contraindicated in
patients with severe pulmonary hypertension (systolic pulmonary artery [PA] pres-
sure > 60 mm Hg, mean PA pressure > 40 mm Hg) and in patients with moderate
pulmonary hypertension (systolic PA pressure 45-60 mm Hg, mean PA pressure
35-40 mm Hg) when right ventricular dysfunction is present. Screening for pul-
monary hypertension is best accomplished by electrocardiography (right axis
deviation, right ventricular hypertrophy, right ventricular strain), chest radiography
(prominent PA), and questioning the patient for symptoms like fatigue, dyspnea on
exertion, substernal chest pain, and hemoptysis. Evaluation is done by transthoracic
echocardiography, and the diagnosis is confirmed by right heart catheterization.

**Pulmonary System**

Routine preoperative evaluation should include chest radiograph. Pulmonary
function tests and blood gas analysis should be done when indicated. Lung
dysfunction can be independent from liver disease or can be the direct result of
severe liver disease. Intrinsic pulmonary dysfunction in patients with severe liver
disease, such as emphysema or asthma has the same incidence as in patients
without liver disease. The severity of these irreversible diseases should be
considered when accepting a patient for transplantation. However, some lung
dysfunction is the direct result of liver disease. Restrictive pulmonary disease can
be the result of tense ascites or pleural effusion, which is especially common on
the right side.

Hepatopulmonary syndrome is a condition that is unique to severe liver
disease: it is the result of abnormally dilated precapillaries and capillaries in the
pulmonary circulation, leading to significant ventilation/perfusion mismatch and
hypoxia. Dilated capillaries are more common in the bases of the lungs, leading to
orthodeoxia (lower arterial pO₂ in the upright position). Oxygen administration
improves oxygenation, which should not occur in situations with right-to-left
shunting. However, injection of agitated saline (echogenic contrast) during
echocardiography shows the contrast in the left atrium and ventricle about 3-4
cardiac cycles after their presence in the right atrium or ventricle, suggesting the
presence of an intrapulmonary right-to-left shunt. This combination is unique to
hepatopulmonary syndrome. Thus, the condition is confirmed by contrast-
enhanced echocardiography, and pulmonary angiography or radionuclide scan-
ning is rarely necessary to confirm the diagnosis. The presence of the
hepatopulmonary syndrome is not a contraindication to liver transplantation,
because the syndrome is reversible after successful transplantation, although many
have a prolonged recovery in the intensive care unit.

Central Nervous System
Cerebral function can be affected because of an excess of metabolites that are
normally metabolized by the liver or because of abnormal metabolites. Hepatic
encephalopathy, common in acute fulminant failure, has been attributed to
abnormal ammonia metabolites. However, other factors contribute to hepatic
encephalopathy: cerebral edema, changes in neurotransmitter concentrations and
blood-brain barrier function, decreased cerebral metabolic rate, uncoupling of
cerebral blood flow, and increased intracranial pressure. By itself, encephalopathy
is not a contraindication to liver transplantation, but if severe it may require
tracheal intubation for airway protection. Seizures and subarachnoidal bleeding
also can affect consciousness. Evaluation includes the use of computed tomography
scans of the head, electroencephalography, transcranial Doppler blood flow
determination, and epidural intracranial pressure determination.

Renal System
Renal dysfunction may be the result of hypovolemia, acute tubular necrosis,
terminal renal disease, or hepatorenal syndrome. The hepatorenal syndrome is
caused by abnormal distribution of renal blood flow, due to hormonal imbalances,
resulting in low urine output, a low urinary sodium concentration (< 5 mmol/L)
and a high urine/plasma creatinine ratio. The hepatorenal syndrome is reversible
after successful transplantation. Patients with non-reversible renal failure should
be considered for combined liver-kidney transplantation.
Acid-Base Balance and Electrolytes

Diuretic therapy can result in intravascular volume depletion, hyponatremia, and hypokalemia. Excessive antidiuretic hormone activity can contribute to the hyponatremia, which should be corrected very slowly to avoid central pontine myelinolysis. Hypokalemia rarely requires potassium administration. Hyperkalemia can be present in patients with renal failure, and usually requires dialysis. Metabolic alkalosis is due to hypokalemia and drainage of gastric secretions, and metabolic acidosis can be the result of compromised tissue perfusion in severely ill patients. Correction of all these problems is difficult preoperatively.

Carbohydrate Metabolism

Hypoglycemia can occur with fulminant hepatic failure. Chronic liver disease may lead to insulin resistance and high glucagon levels, although hyperglycemia is rarely seen.

Hematology and Coagulation

Almost all candidates for liver transplantation have synthetic liver dysfunction, and therefore have coagulopathy as a result of decreased production of coagulation factors (especially factors II, V, VII, IX, and X). Fibrinogen levels may be high, normal, or low. In addition, portal hypertension leads to sequestration of platelets in the spleen, and therefore thrombocytopenia contributes to the coagulopathy. However, coagulation changes are complex because the liver also produces inhibitors of coagulation and fibrinolytic proteins (plasminogen and alpha2-antiplasmin), and because activated coagulation factors are normally cleared by the liver. This may lead to varying degrees of disseminated intravascular coagulation. Correction of the coagulopathy is best done intraoperatively, except when patients are bleeding acutely or when coagulopathy is extreme (prothrombin time [PT] > 20 s, platelet count < 20,000,000/mL). Anemia may be the result of continuing gastrointestinal bleeding, erythrocyte destruction in the spleen, and reduced production in the bone marrow. Preoperatively patients need routine hemostatic evaluation, with special analyses for items such as preexisting red cell alloantibodies. If HLA antibodies are present they will not only affect graft survival but also reduce in vivo yields of transfused platelets, unless special products are selected. Patients with broadly reactive red cell or HLA antibodies require careful preoperative planning between surgeons, anesthesiologists, and coagulation/transfusion specialists. Rare circulating anticoagulants can sometimes be managed by preoperative plasmapheresis.

ANESTHETIC MANAGEMENT

Pharmacokinetic and Pharmacodynamic Changes

The pharmacology of many anesthetics is changed in the presence of liver disease and during liver transplantation. This is the result not just of altered metabolism by the liver, changes in liver blood flow, and drug protein binding, but also by changes in the volume of distribution of the drugs. However, this usually does not interfere significantly with the use of anesthetics intraoperatively,
because although the duration of action of many of the anesthetics may be prolonged, most patients after liver transplantation are not extubated immediately but require a postoperative ventilation period of at least a few hours. Similarly, the pharmacodynamic changes that may occur are handled by titrating the drugs to effect. Therefore, unless massive drug overdosing occurs, the altered pharmacology is only relevant if the anesthesiologist wants to extubate the patient at the end of the procedure.

**Preoperative Preparation**

The anesthesia team should be experienced; at least two anesthesia providers and an experienced anesthesia technician should be available. The blood bank should be prepared to supply packed red blood cells, fresh frozen plasma, cryoprecipitate, and platelets in large quantities. Special equipment should be available, and is presented in Table 1. The operating room table and the arm boards should be padded to avoid nerve or skin injury.

**Induction and Maintenance of Anesthesia**

One of the main concerns is the possibility of aspiration of gastric contents after induction of anesthesia but before tracheal intubation. Patients with liver disease, severe ascites, and/or recent gastrointestinal bleeding may not have an empty stomach. Therefore, cricoid pressure is routinely applied during induction of anesthesia. Most commonly thiopental, propofol, or etomidate are used to induce anesthesia, and succinylcholine provides the most rapid paralysis permitting fast intubation. Nondepolarizing muscle relaxants have been used in patients with hyperkalemia.

Maintenance of anesthesia is accomplished with a combination of intravenous narcotics (e.g., fentanyl), benzodiazepines (e.g., midazolam, lorazepam), muscle relaxants (e.g., pancuronium, cisatracurium), and inhaled anesthetics (e.g., isoflurane, desflurane). Cardiovascular drugs such as lidocaine, atropine, dopamine, epinephrine (10 µg/mL and 100 µg/mL) should be available. Other drugs that should be available include epsilon-aminocaproic acid, protamine sulfate, calcium

<table>
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<th>Table 1. Equipment required for liver transplantation anesthesia</th>
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<tr>
<td>Anesthesia machine with air supply</td>
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<td>Multichannel patient monitor with pulse oximeter</td>
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<td>Multigas analyzer</td>
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<td>Cardiac output monitor</td>
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<tr>
<td>Cardiac defibrillator</td>
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<tr>
<td>Drug infusion pumps</td>
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<tr>
<td>Warming blanket</td>
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<tr>
<td>Forced air warmer</td>
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<td>Heated humidifier</td>
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<tr>
<td>Rapid infusion system</td>
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<tr>
<td>Autotransfusion system</td>
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<tr>
<td>Thromboelastographs (TEG)</td>
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<td>Transesophageal echocardiography (TEE)</td>
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chloride, sodium bicarbonate, tromethamine (THAM), dextrose, and insulin. Positive end-expiratory pressure (5 cm H₂O) is frequently applied to improve oxygenation in the presence of tense ascites and upper abdominal retractors and to prevent atelectasis. The humidification of inspired gases, a forced air warmer, increasing the room temperature, and appropriate draping by the surgeon in order to prevent the patient to become wet may all aid in the prevention of hypothermia.

**POSTINDUCTION PREPARATION**

Arms are extended at a 90° angle in an attempt to avoid brachial plexus injury. An orogastric tube is placed to drain gastric secretions; nasogastric tubes are avoided to reduce the chance of nasal bleeding. Two large-bore intravenous catheters (7-8.5 Fr) are placed after induction of anesthesia to allow blood transfusion. The choice of veins for these catheters depends on whether venovenous bypass is used; in general the antecubital vein on the side where the axillary vein is cannulated for venovenous bypass is avoided. Also, subclavian veins are only used as a last resort because accidental subclavian arterial puncture may lead to intrathoracic bleeding in patients with significant coagulopathy. The most commonly used veins are the right antecubital vein and the internal jugular veins, with the external jugular veins as acceptable alternatives.

The radial arterial catheter is usually inserted after induction of anesthesia unless the patient is hemodynamically unstable. An additional femoral arterial catheter is placed because it gives more accurate information regarding central aortic pressure, especially during the anhepatic state and immediately after graft reperfusion. A pulmonary artery catheter is placed, most frequently through an internal jugular vein; commonly the pulmonary artery catheter has been modified to determine mixed-venous oxygen saturation, while another modification allows continuous cardiac output, or right ventricular ejection fraction and end-diastolic volume determination (RVEDV). Intermittent determination of arterial blood gas tension, acid-base status, electrolytes (including ionized calcium) and hematocrit or hemoglobin is obligatory.

**INTRAOPERATIVE LABORATORY TESTS**

The tests presented in Table 2 should be performed every hour, or more frequently when indicated. Tests should be performed at the following times: baseline, every hour thereafter, 5 min after onset of anhepatic state, every 30 min during anhepatic state, 15 min before graft reperfusion, 5 and 30 min after graft reperfusion, and then every hour. Many institutions use thromboelastography (TEG) instead of or in addition to more standard coagulation tests.

**INTRAOPERATIVE CARE**

The liver transplantation procedure is divided into three stages: the preanhepatic, anhepatic, and neohepatic stage. Surgeons may use venovenous bypass to decompress the inferior vena cava and portal vein during the anhepatic stage of the procedure when the inferior vena cava and portal vein are clamped. Some surgeons use it never; others use it only if the patient does not readily tolerate a trial clamping
of the inferior vena cava; and yet others use it in virtually all patients. Another
technique is side-clamping of the inferior vena cava to allow end-to-side anasto-
omosis of donor cava to recipient cava (piggy-back technique). Although this tech-
nique was designed to maintain flow in the inferior vena cava, the side-clamping
usually results in a significant reduction in blood flow. Venovenous bypass is in-
frequently used in pediatric liver transplantation.

HEMODYNAMIC MANAGEMENT
Most anesthesiologists feel that the circulation has to be maintained hyperdy-
namic perioperatively in order to maintain tissue perfusion. However, this may
not be possible during the anhepatic stage, because venous return is significantly
reduced when the inferior vena cava is clamped, even if venovenous bypass is
used. During the preanhepatic stage, hypotension is most commonly due to
hypovolemia related to bleeding and insensible fluid losses, and is treated by fluid
administration. Ionized calcium concentrations should be normalized by the
administration of calcium chloride. Determination of RVEDV and transesophageal
echocardiography (TEE) may help when the interpretation of more routine
hemodynamic monitoring is difficult. Small amounts of vasoconstrictors/inotropic
agents (dopamine, epinephrine) are rarely necessary to maintain an adequate
perfusion pressure.

During the anhepatic stage, when cardiac output is lower, there is a com-
pensatory increase in systemic vascular resistance, usually resulting in preserved
blood pressure. There are several different surgical techniques of handling the
inferior vena cava during this stage: simple cross-clamping, side-clamping of the
inferior vena cava (piggy-back), and the use of venovenous bypass. The latter
 techniques result in a smaller decrease in the heart’s preload. On graft reperfusion,
there is more of an increase in venous return with the simple cross-clamping
technique, and therefore fluid management before unclamping of the vessels and
graft reperfusion has to take this into account to prevent hypervolemia after graft
reperfusion.

The neohepatic stage starts with unclamping of the portal vein and inferior
vena cava. Graft reperfusion is usually associated with a severe reduction in
systemic vascular resistance and an increase in venous return, leading to arterial
hypotension in about 30% of the patients. This post-reperfusion syndrome
is probably the result of the sudden release of cold, acid, and hyperkalemic solution
from the graft, but probably other released substances play a role as well. Usually
myocardial contractility seems to be preserved, but some patients may develop
short-lived myocardial depression. The post-reperfusion syndrome responds

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Table 2. Laboratory tests during liver transplantation

<table>
<thead>
<tr>
<th>Test</th>
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<tbody>
<tr>
<td>Arterial blood gas analysis and acid-base state</td>
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<tr>
<td>Electrolyte levels (Na⁺, K⁺, Ca²⁺, Cl⁻)</td>
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<tr>
<td>Blood glucose level</td>
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<tr>
<td>Thromboelastography (TEG)</td>
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<tr>
<td>Platelet count, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen</td>
</tr>
</tbody>
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readily to small amounts of epinephrine (10-50 µg). However, severe bradycardia or even sinus arrest within the first few minutes after graft reperfusion has been seen in a few patients, but fortunately is quickly reversed by boluses of epinephrine (100-250 µg) and chest compressions.

During the remainder of the neohepatic stage, cardiac output returns to the values seen during the preanhepatic stage. Sometimes excessive vasodilation associated with graft reperfusion persists for 1-2 h, requiring low-dose epinephrine or dopamine infusion. Normally, the graft starts to be metabolically active very early after reperfusion, and therefore CaCl₂ and NaHCO₃ are rarely necessary to maintain a normal metabolic state.

**FLUID AND TRANSFUSION MANAGEMENT**

Maintaining normovolemia intraoperatively is probably the most important task for the anesthesiologist. At the same time, it is probably also the most difficult task. The main reason for maintaining the patient’s volume status is that this is the only way for the cardiovascular system to remain hyperdynamic during the procedure. Cardiac filling pressures may not accurately reflect the volume status of the patient, because the compliance of the heart and thoracic cage changes significantly during the transplant as the result of the use of retractors and varying pressure on the diaphragm. TEE and determination of RVEDV probably allow a more accurate estimation of the patient’s volume status.

Although the average blood loss has gradually decreased over the last 15 years, it is impossible to predict blood loss in individual patients. Indeed, blood loss can still be substantial (more than 10 times blood volume). Intraoperative autologous transfusion (cell saver) may reduce the need for packed red blood cells from the blood bank. However, virtually all coagulation factors and platelets are removed during the process. Most anesthesiologists aim for a hematocrit of 25-30%, which should be sufficient to provide adequate oxygen transport. Because most patients have coagulopathy, one unit of fresh frozen plasma is usually administered for each unit of transfused packed cells. More fresh frozen plasma may be necessary to correct coagulopathy. Cryoprecipitate and platelets are given based on coagulation tests. Most liver transplant anesthesiologists use a type of rapid infusion device to allow transfusion of large amounts of fluids and blood products, allowing for adequate warming of the solution. Transfusion devices ideally should have air detectors to avoid intravenous infusion of air. A commonly used transfusion system is the Rapid Infusion System® (Haemonetics, Inc. Braintree, Mass.) (Fig. 1). This device allows transfusion of up to 1.5 L/min of a warmed blood mixture.

**COAGULATION MANAGEMENT**

Intraoperative coagulopathy is the result of preoperative coagulopathy, thrombocytopenia, and platelet dysfunction; intraoperative dilution of coagulation factors and platelets; excessive fibrinolysis; and hypothermia. Although the coagulopathy that occurs during liver transplantation usually can be corrected by transfusion of fresh frozen plasma, cryoprecipitate, and platelets, pharmacologic intervention may allow normalization of the coagulation with less blood products and reduced time for complete surgical hemostasis. Blood coagulability is determined
by TEG, platelet count, and routine coagulation tests (PT, PTT, fibrinogen level), but observation of the surgical field reveals invaluable information. TEG measures global hemostasis of plasma proteins and platelet interactions. Only TEG shows fibrinolysis in a timely manner. In addition, TEG allows the in-vitro use of pharmacologic intervention, greatly expanding the value of this monitoring technique (Figs. 2, 3). However, some feel that TEG lacks the specificity for guiding blood component replacement that is found with measuring platelets, fibrinogen, PT, and PTT. Thus in problem cases both systems may have a role. The frequency of hemostasis testing is determined by the degree of coagulation dysfunction, the degree of surgical difficulty, and the surgical field.

Blood component therapy is based on hemostatic testing, TEG, and adequacy of surgical hemostasis. When component replacement is indicated, it should be done to a level of adequacy, not normality. Patients may have successful transplants with only moderate blood loss with platelet counts of 40-50,000,000/mL or fibrinogen concentrations of 100-125 mg/dL. When fibrinolysis is present, epsilon-aminocaproic acid is frequently used for reversal, and some programs use continuous administration for prophylaxis. In either approach very low doses are usually effective (single dose 250-500 mg). Aprotinin has been advocated, with some data suggesting decreased blood loss. Others are concerned about the potential for thrombosis with the prophylactic use of antifibrinolytic agents, and additional research is required. After graft reperfusion, heparinoid effect can be seen even after flushing of the donor organ, but protamine reversal is rarely necessary.

Unfortunately, the coagulation changes during liver transplantation are incompletely understood: although activation of the fibrinolytic system has been

well documented, especially during the anhepatic state and immediately following
graft reperfusion, it is possible that there is also activation of the coagulation system
in some patients, possibly leading to intravascular coagulation. Pulmonary
thromboembolism has been reported in some patients.

**METABOLIC MANAGEMENT**

Ionized hypocalcemia is a recognized complication of blood transfusion in pa-
tients with liver failure because of their decreased ability to metabolize citrate.
Patients undergoing liver transplantation may develop hypocalcemia when trans-
fused during the preanhepatic and anhepatic stage, requiring calcium chloride
administration. Hyperkalemia may develop in patients undergoing massive trans-
fusion or having renal failure. This is best treated with glucose and insulin, which
forces potassium into the cells, or washing of the red blood cells to reduce the
potassium load. Metabolic acidosis is more common in patients with liver disease,
especially when there is tissue hypoperfusion or massive transfusion. Sodium
bicarbonate may increase sodium levels too quickly, possibly resulting in central
pontine myelinolysis. However, tromethamine (THAM) also corrects metabolic
acidosis but does not contain sodium, and therefore the use of tromethamine
(THAM) contributes to the correction of metabolic acidosis but at the same time
can ameliorate the hypernatremic effects of sodium bicarbonate. Ionized hypo-
magnesemia has been documented, but its clinical consequences are unknown.
Therefore, the administration of magnesium sulfate is still controversial.

**SELECTED READINGS**

1. Marquez J, Martin D, Virji MA et al. Cardiovascular depression secondary to ionic
hypocalcemia during hepatic transplantation in humans. Anesthesiology 1986;
65:457-461.
3. Krowka MJ, Cortese DA. Hepatopulmonary syndrome: an evolving perspective in
4. De Wolf AM, Begliomini B, Gasior T et al. Right ventricular function during liver

**HEART TRANSPLANTATION**

The number of heart transplant procedures has exploded in the mid-1980s,
making heart transplantation a well-established and standardized procedure
today. Because of the shortage of organ donors, this increase has now reached a
plateau. The one-year survival rate is currently > 80%, with most survivors
returning to a fairly normal active lifestyle. One of the main concerns for the
anesthesiologist is to get the patient safely onto cardiopulmonary bypass without
further damage to any of the other essential organs.

**PREOPERATIVE EVALUATION**

Most candidates for heart transplantation have end-stage cardiac failure as a
consequence of ischemic or idiopathic cardiomyopathy. Other indications for heart
transplantation include terminal valvular lesions and congenital anomalies that
are not amenable to other surgical or medical therapy. Symptoms include severely limited physical activity and shortness of breath with limited activity or at rest. Recipients are usually < 60 years old, should be healthy otherwise or have organ dysfunctions that are reversible after heart transplantation, and should be compliant with medical instructions.

**Cardiovascular System**

Patients with end-stage cardiac disease have low cardiac outputs and high filling pressures despite optimal medical management. The initial response to left ventricular dysfunction is an increase in left ventricular end-diastolic volume; this may temporarily restore stroke volume at the cost of an increase in left atrial pressure. Eventually right atrial pressure will increase also, leading to the classic signs and symptoms of congestive heart failure. In addition, the systemic vascular resistance may increase in an attempt to maintain blood pressure. Atrial arrhythmias are common, and some patients with ventricular arrhythmias may have received an automatic implantable cardiac defibrillator (AICD).

Preoperative evaluation should include right and left heart catheterization to evaluate the pulmonary circulation and accurately determine intracardiac pressures. A pulmonary vascular resistance > 6 Wood units is a contraindication for heart transplantation because it frequently leads to failing of the right ventricle of the newly transplanted heart; these patients may be candidates for combined heart-lung transplantation. Moderate increases in pulmonary vascular resistance are usually tolerated if the transplanted heart functions well.

The dilated cardiomyopathy can lead to mural thrombi, which may be treated with chronic anticoagulation. Coronary angiography may determine the presence of treatable coronary lesions. Patients may receive pharmacologic support, frequently consisting of a combination of vasodilators and inotropic agents. Alternatively, a circulatory assist device may be in place (intraaortic balloon counterpulsation, ventricular assist device, artificial heart). Importantly, the prolonged low cardiac output and venous congestion will affect the function of other organs, and therefore all organ systems have to be evaluated preoperatively.

**Pulmonary System**

Prolonged left ventricular dysfunction results in increased left atrial and pulmonary venous pressure, which leads to an increase in pulmonary vascular resistance caused by hypertrophy of the musculature of the pulmonary arteries. The increase in left atrial pressure also results in an increase in lung water, causing ventilation/perfusion mismatch, increased airway resistance, decreased lung compliance, and increased work of breathing. Pleural effusions will reduce functional residual capacity and possibly further impair oxygenation.

**Hepatic System**

Chronic passive congestion of the liver may result in a reduced production of coagulation factors and other proteins. In addition, drug metabolism may be altered.
Gastrointestinal System
Like most other patients undergoing transplant procedures, these patients are considered to have full stomachs, not just because of the possible recent food intake, but also because some patients ingested immunosuppressants just before arriving in the operating room. Also, the high catecholamine concentrations may lead to reduced gastric emptying.

Renal System
Renal dysfunction is common as a result of low cardiac output and the aggressive use of diuretics to treat congestive heart failure. The use of diuretics may also result in hyponatremia and hypokalemic metabolic alkalosis, which may require potassium replacement. Similarly, hypomagnesemia can lead to arrhythmias and may require supplemental therapy with magnesium sulfate.

Anesthetic Management
The single most important aspect of anesthetic management is to avoid further deterioration of the circulatory system, attempting to preserve the function of other organ function until cardiopulmonary bypass is started. Therefore, myocardial depressant drugs are avoided and increasing inotropic support may be necessary.

Pharmacokinetic and Pharmacodynamic Changes
Although the liver dysfunction and the changes in volume of distribution may be altered, this usually does not require a significant change in drug dosing intraoperatively.

Immediate Preinduction Preparation and Monitoring
Premedication is frequently avoided, not just because these patients are more sensitive to sedatives, but also because these patients are usually well-informed regarding their procedure, and therefore tolerate the transfer to the operating room very well. The anesthesia equipment that is used for routine cardiac procedures should be sufficient for heart transplants. Monitoring includes electrocardiography (leads II and V5), pulse oximetry, and multigas analysis. Urine output is followed. Bladder/rectal, esophageal, and pulmonary arterial temperature are measured. A femoral arterial catheter is placed before induction of anesthesia to allow determination of central aortic pressure, because there may be a discrepancy between radial arterial and central aortic pressure, especially immediately after cardiopulmonary bypass. An oximetric pulmonary artery catheter is inserted through the right internal jugular vein, allowing continuous mixed-venous oxygen saturation (SvO₂) measurement. Cardiac output is determined using thermodilution technique. A long sheet is used to cover the pulmonary artery catheter, which allows it to be pulled back into the superior vena cava during cardiopulmonary bypass and readvanced into the pulmonary artery after cardiopulmonary bypass. A transesophageal echocardiography (TEE) probe is placed after induction of anesthesia, and allows for additional monitoring of cardiac function and volume status.
Induction and Maintenance of Anesthesia

Communication with the surgical team is essential before starting induction of anesthesia in order to decrease ischemic time of the organ. The timing should take into consideration the longer surgical time needed in patients undergoing reoperation.

Frequently, the induction and maintenance of anesthesia does not differ much from the techniques used in other patients with poor cardiac function undergoing cardiac anesthesia. However, cricoid pressure is usually applied to prevent aspiration of gastric contents. A combination of narcotics (e.g., fentanyl, sufentanil) and muscle relaxants (e.g., pancuronium, rocuronium, cisatracurium) is administered, and their hemodynamic effects are followed carefully. Narcotics are administered until loss of consciousness. The choice of muscle relaxants depends mainly on the desired change in heart rate. Alternatively, a hypnotic agent that is devoid of myocardial depressant effects (etomidate) has been used with succinylcholine to provide rapid intubating conditions.

Although the anesthetic agents that are used have no significant direct hemodynamic effects, the loss of consciousness by itself may lead to a reduction in sympathetic output from the brain stem and circulating catecholamines, leading to hypotension as a result of systemic vasodilation and possibly a further decrease in myocardial contractility. In addition, venous dilatation may exacerbate the mildly hypovolemia that is frequently present as a result of aggressive diuretic therapy. Therapy of hypotension during induction of anesthesia is usually guided by the hemodynamic monitoring: vasodilation may be treated with volume administration and small amounts of vasoconstrictors (e.g., phenylephrine 50-100 µg boluses), while reductions in myocardial contractility can be treated with inotropic agents (e.g., dopamine or dobutamine 3-5 µg/kg/min). More accurate monitoring and therefore also more directed treatment can be initiated once the TEE probe has been placed after tracheal intubation. It has to be recognized that volume therapy can exacerbate congestive heart failure, and that vasoconstrictors can increase left ventricular afterload and therefore decrease cardiac output. Also, catecholamines can lead to arrhythmias which are frequently poorly tolerated in these patients. Reaction to intubation or surgical stimulation can be different from that seen in other patients: light anesthesia may not be reflected as hypertension and tachycardia, but merely as a decrease in cardiac output, an increase in pulmonary capillary wedge pressure and systemic vascular resistance, and a decrease in Svo₂. This requires additional anesthetics or the use of vasodilators (nitroglycerine or nitroprusside).

Anesthesia is maintained with a combination of narcotics (e.g., fentanyl 50-100 µg/kg followed by 5-10 µg/kg/h, or sufentanil 10-15 µg/kg followed by 1-2 µg/kg/h), muscle relaxants, and amnestic agents (e.g., midazolam 5-10 mg, lorazepam 2-4 mg). However, the addition of benzodiazepines to high-dose narcotics may be associated with mild reductions in cardiac output and systemic vascular resistance, resulting in hypotension. Low-dose dopamine, mannitol and diuretics (furosemide) are frequently used intraoperatively, especially in patients with preoperative renal dysfunction. However, there is little evidence that this management improves postoperative renal function.
**Liver and Intestinal Transplantation**

**INTRAOPERATIVE CARE**

**Cardiopulmonary Bypass**

Anticoagulation is achieved with normal doses of heparin (300 U/kg) prior to cardiopulmonary bypass. Some patients with hepatic congestion or prolonged heparin administration preoperatively may have reduced plasma concentrations of antithrombin III and therefore may be resistant towards the effects of heparin. Heparin resistance is promptly corrected by administration of antithrombin III (1000-1500 U), although giving 1-2 units of fresh frozen plasma is an acceptable alternative. The aorta is cannulated in the normal fashion. The pulmonary artery catheter is withdrawn into the superior vena cava, and the superior and inferior vena cava are cannulated separately to allow excision of the heart. After initiation of cardiopulmonary bypass, the aorta, pulmonary artery, and atria are transected and the heart is excised, leaving a cuff of the right and left atrium to allow anastomosis to the donor right and left atrium. This is followed by anastomosis of the aorta and pulmonary artery, and after rewarming the patient is weaned from cardiopulmonary bypass.

**Weaning from Cardiopulmonary Bypass**

The patient is weaned from cardiopulmonary bypass using the same principles as those for any cardiac procedure. Thus, heart rate and rhythm, volume status, contractility, and afterload are optimized. This frequently requires the administration of isoproterenol, dopamine, or dobutamine. The choice of agent is mainly determined by the systemic vascular resistance. The volume management is guided by the filling pressures and TEE. Direct observation of the heart in the surgical field reveals right ventricular function. After weaning, the pulmonary artery catheter is readvanced into the pulmonary artery. Appropriate monitoring will allow the anesthesiologist to determine whether weaning from cardiopulmonary bypass is successful. Adequate circulation results in a cardiac index of > 2 L/min/m² and a SvO₂ of > 70%.

**Management after Cardiopulmonary Bypass**

Most transplanted hearts depend on the exogenous administration of catecholamines for the first few days after transplantation. Therefore, their administration should not be interrupted at any point, especially during and immediately after the transfer of the patient to the intensive care unit.

Biventricular failure immediately after transplantation can be the result of inadequate preservation or hyperacute rejection, and may require inotropic support, biventricular assist device, or artificial heart. Right ventricular failure can be seen in patients with mild-moderate pulmonary hypertension. Excessive volume loading should be avoided; maintaining perfusion of the right ventricle by optimizing blood pressure and inotropic support is essential. A right ventricular assist device may be required.
LUNG TRANSPLANTATION

Candidates for lung transplantation include patients with end-stage pulmonary disease but preserved right and left ventricular function. Pulmonary diseases include restrictive, obstructive, infective, and pulmonary vascular. Most candidates for single lung transplantation have pulmonary fibrosis, emphysema, chronic obstructive pulmonary disease, and alpha1-antitrypsin deficiency. Patients with pulmonary hypertension who do not yet have right ventricular failure may also be acceptable candidates for single lung transplants. A double lung transplant is performed when leaving one diseased lung in place would lead to complications (chronic bilateral infection such as cystic fibrosis and bronchiectasis, or severe air trapping).

Heart-lung transplantation is indicated in patients with end-stage pulmonary vascular disease that can be the result of cardiac lesions (e.g., Eisenmengers’ syndrome) or pulmonary disorders (e.g., pulmonary hypertension), resulting in irreversible failure of both heart (right or left ventricle) and lungs.

The main intraoperative problems include hypoxemia, hypercarbia, and right ventricular failure.

PREOPERATIVE EVALUATION

Pulmonary System

Pulmonary function tests and ventilation/perfusion scans will help in the determination which lung is diseased the most. Most patients require supplemental oxygen to improve oxygenation, although most are still mildly hypoxic. Hypercarbia is common. Patients with little or no functional reserve may be more prone to hemodynamic instability during induction of anesthesia.

Cardiovascular System

Right ventricular function has to be determined, especially in patients with pulmonary hypertension. The degree of right ventricular dysfunction and its potential reversibility will determine what type of procedure is indicated and whether the patient is likely to require cardiopulmonary bypass. This is usually accomplished by echocardiography or radionuclide scans. In addition, left ventricular failure or coronary artery disease should be excluded.
Hepatic System
As in candidates for heart transplantation, passive congestion of the liver may result in decreased synthesis of proteins and drug metabolism.

Surgical Procedure
Single vs. Double Lung Transplant
The preferred procedure in most patients is single lung transplantation. A posterolateral thoracotomy is performed with the patient in the lateral position, but with one groin exposed to allow cannulation of femoral vessels for cardiopulmonary bypass. If double lung transplantation is indicated, it is usually accomplished using sequential single lung transplants using the clamshell thoracosternotomy in the supine position. Again, at least one groin is exposed. The native lung with the most severe pathology should be transplanted first.

Need for Cardiopulmonary Bypass
Cardiopulmonary bypass is avoided if possible because it prolongs the procedure, and results in more perioperative blood loss and an increased need for platelets and coagulation factors after cardiopulmonary bypass. The decision to use cardiopulmonary bypass is based on the right ventricular function after clamping of the pulmonary artery of the lung that is excised. If cardiac output after clamping of the pulmonary artery decreases significantly and/or if worsening right ventricular dysfunction is observed on transesophageal echocardiography (TEE), it is very likely that cardiopulmonary bypass will be necessary. Most patients with pulmonary hypertension will require cardiopulmonary bypass because the right ventricle does not tolerate a further increase in afterload. Also, the patients with pulmonary hypertension who will need correction of cardiac anomalies (e.g., atrial septum defect, ventricular septum defect) will require cardiopulmonary bypass. Finally, cardiopulmonary bypass is used when there is intractable hypoxia during one-lung ventilation, despite appropriate interventions. Use of femoral cannulas to establish partial cardiopulmonary bypass may be adequate treatment for right ventricular failure. However, there is still blood flow through the native lung and ejection by the left ventricle, and therefore oxygenation of arterial blood in the upper half of the body is sometimes inadequate. Therefore, determination of PaO₂ from a blood sample from a radial artery has to be done to assure adequate oxygenation of blood perfusing the heart and brain. Measures should be instituted to improve oxygenation of blood flowing through the native lung. If necessary, ventricular fibrillation is induced during cardiopulmonary bypass in order to interrupt flow through the native lung.

Anesthetic Management
Preoperative sedation is minimal because these patients have limited cardiopulmonary reserve. Intravenous catheters are usually placed in upper extremities. However, in patients undergoing sequential double lung transplantation using the clamshell thoracosternotomy who will have both arms bent at the elbows and suspended from the ether screen, catheters in antecubital veins
are avoided. After the recipient is transferred to the operating room, a right radial arterial catheter is placed. In patients who are likely to require cardiopulmonary bypass a femoral arterial catheter is also inserted. An oximetric pulmonary artery catheter is usually placed after induction of anesthesia. Standard non-invasive monitoring includes electrocardiography (lead II and V5), blood pressure cuff, pulse oximetry, and multigas analysis. TEE is very helpful in the evaluation of volume status and right ventricular function, and may help in the evaluation of the vascular anastomoses.

Anesthetic induction should keep the patient’s recent oral intake into consideration. Because these procedures are done with little notice, cricoid pressure usually has to be applied. In patients with compromised right ventricular function, anesthetic agents that do not depress cardiac function are used (e.g., fentanyl, sufentanil, etomidate, muscle relaxants, benzodiazepines). In patients with preserved right ventricular function, low concentrations of inhaled anesthetics are usually well tolerated.

Single Lumen Endotracheal Tube vs. Double-Lumen Tube

Double lung transplants performed on cardiopulmonary bypass usually receive a single lumen endotracheal tube. All other patients will require a double-lumen tube, and its correct position is verified using fiberoptic bronchoscopy.

Management of Hypoxemia

Hypoxemia can occur at any time during lung transplantation, but is most common during one-lung ventilation. Hypoxemia is most severe about 20 min after initiation of one-lung ventilation, and initial treatment should include judicious use of positive end-expiratory pressure (PEEP) to the ventilated lung, oxygen insufflation to the non-ventilated lung, and clamping of the pulmonary artery of the nonventilated lung. Pneumothorax on the ventilated side should always be considered. If hypoxia is refractory to all interventions, cardiopulmonary bypass should be initiated.

Management of Mechanical Ventilation

Mechanical ventilation in patients undergoing lung transplantation can result in air trapping due to incomplete exhalation, especially in patients with obstructive pulmonary disease. Significant air trapping may lead to increases in intrathoracic pressure and hemodynamic compromise because of a reduction in venous return. This problem can be diagnosed by disconnecting the patient from the breathing circuit for about 30 seconds; the blood pressure will return to baseline if the cause of hemodynamic instability was hyperinflation of the lungs and air trapping. This is best treated with increasing expiratory time, resulting in hypoventilation and permissive hypercapnia, which is usually well tolerated as long as oxygenation can be maintained.

Mechanical ventilation with or without PEEP in any patient may lead to an increase in pulmonary vascular resistance. This may not be tolerated well in patients with right ventricular dysfunction. Increasing the volume status may not be the best intervention; inotropic support may have better results. The use of
pulmonary vasodilators in these circumstances is frequently not very effective. It is important to maintain coronary perfusion pressure in order to preserve the oxygen supply to the right ventricle.

Sudden reductions in oxygen saturation and hypotension can be the result of tension pneumothorax, especially in patients with bullous disease or fibrotic lungs.

After reperfusion, the transplanted lung may dysfunction, or the native lung may not tolerate PEEP or develop air trapping; this situation requires differential lung ventilation. However, if the transplanted lung functions well, the double lumen endotracheal tube is replaced by a single lumen tube at the end of the procedure.

**Coagulopathy**

Coagulopathy may be induced by cardiopulmonary bypass, although lung transplantation by itself may be associated with activation of the coagulation and fibrinolytic systems. Thus, double lung transplantation and use of cardiopulmonary bypass is associated with more significant bleeding, and frequently requires platelet administration. Aprotinin, epsilon-aminocaproic acid, tranexamic acid, and DDAVP have all been used in lung transplantation.

**Lung Reperfusion**

Some degree of pulmonary edema is common in the transplanted lung after reperfusion. Significant edema requires the use of high levels of PEEP, diuresis, and volume restriction. Severe pulmonary edema requires differential lung ventilation, or in the case of double lung transplantation, the use of extracorporeal membrane oxygenation.

**Postoperative Analgesia**

A thoracic epidural catheter may be placed preoperatively in patients with a very low chance for cardiopulmonary bypass. However, more frequently, the epidural catheter is placed early postoperatively after correction of any persisting coagulopathy.

**Selected Readings**


**Kidney Transplantation**

Although chronic dialysis improves life expectancy, kidney transplantation improves the quality of life. Therefore, kidney transplantation has now become a commonly performed and standardized surgical procedure. Patients with end-stage renal disease but with otherwise normal life expectancy are good candidates for this procedure. The tolerable ischemic time for kidneys is up to 48 h, and therefore cadaveric kidney transplants are semi-elective procedures, while living-related kidney transplants are elective.
PREOPERATIVE EVALUATION

Renal failure ultimately results in the uremic syndrome: these patients are unable to regulate their volume status and composition of body fluids, leading to fluid overload, metabolic acidosis, and hyperkalemia. In addition, there is secondary organ dysfunction with neuropathy, anemia, platelet dysfunction, hypertension, congestive heart failure, pericardial or pleural effusions, muscle weakness, osteodystrophy, nausea, vomiting, and impaired cellular immunity.

Renal System

Candidates for renal transplantation usually have end-stage renal failure. However, with the advent of living-related kidney transplantation, some of the recipients may have pre-terminal renal disease that does not yet require dialysis. When the patient is treated with dialysis, it is important to determine the volume status and electrolyte concentrations immediately preoperatively.

Electrolyte Changes

Hyperkalemia above 5.5 mmol/L should be corrected by dialysis before the patient is transferred to the operating room. Hypocalcemia may result from decreased intestinal absorption of calcium, resulting in secondary hyperparathyroidism, leading to bone decalcification.

Acid-Base Status

Chronic metabolic acidosis is the result of impaired excretion of hydrogen ions and impaired reabsorption of bicarbonate by the kidneys, and is associated with a compensatory respiratory alkalosis. Severe metabolic acidosis requires dialysis.

Cardiovascular System

Most patients with end-stage renal disease have a hyperdynamic cardiovascular system to compensate for chronic anemia, which is the result of inadequate production of erythropoietin, uremic depression of bone marrow, and erythrocyte membrane fragility. Chronic anemia (hemoglobin levels of 6-8 g/dL) is usually well tolerated and should not require preoperative transfusion. Chronic arterial hypertension is common due to elevated concentrations of renin and angiotensin, and is usually treated with antihypertensive agents such as angiotensin-convert ing enzyme inhibitors, vasodilators, beta-antagonists, and calcium channel blockers. Uncontrolled hypertension can result in hypertensive cardiomyopathy, which may be aggravated by hyperlipidemia. Left ventricular hypertrophy and coronary artery disease are not uncommon. Some of these patients may have silent ischemia as a result of uremic neuropathy. Significant uremic pericarditis is uncommon. Some patients have diabetes mellitus, and therefore the degree of coronary artery disease has to be determined in these patients.

Nervous System

For the anesthesiologist, uremic neuropathy of the sympathetic nervous system may lead to hemodynamic instability and unexpected changes in heart rate and rhythm.
Coagulation System
Coagulopathy may result from thrombocytopenia, abnormal platelet function, and residual heparin effect from hemodialysis.

Anesthetic Management
Pharmacokinetic and Pharmacodynamic Changes
The pharmacology of some anesthetics is changed in the presence of renal failure due to reduced excretion (e.g., pancuronium) or altered protein binding and volume of distribution (e.g., midazolam, diazepam, thiopental). However, the pharmacology of many other anesthetics is not affected to a clinically significant degree, while most drugs are tolerated well if titrated to effect.

Monitoring
Routine monitoring includes electrocardiography, noninvasive blood pressure determination, pulse oximetry, multigas analysis, and peripheral nerve stimulation. For patients with coronary artery disease or poorly controlled hypertension an arterial catheter should be placed to allow continuous blood pressure monitoring and better control of blood pressure. A central venous catheter may be placed after induction of anesthesia to assist in the perioperative volume management, but is only helpful in sicker patients. The central venous catheter is commonly avoided in living-related kidney transplants. A pulmonary artery catheter is rarely indicated. Intraoperative laboratory tests should include determination of hemoglobin or hematocrit, serum electrolytes, blood glucose, and acid-base state.

Induction and Maintenance of Anesthesia
Patients with diabetes may have decreased gastric emptying, and therefore rapid sequence induction should be used. Most commonly used induction agents include thiopental, propofol, and etomidate. Succinylcholine is acceptable if hyperkalemia is not present. Other muscle relaxants that are commonly used are rocuronium and cisatracurium. Anesthesia is maintained with a combination of inhaled anesthetics (e.g., isoflurane, desflurane), narcotics (e.g., fentanyl, sufentanil) and nitrous oxide.

Fluid Management
Most anesthesiologist assure adequate perfusion of the graft by inducing mild hypervolemia and hypertension after revascularization. Fluids are administered to obtain a central venous pressure of 10-15 mm Hg. Achieving a systolic blood pressure of 120-140 mm Hg sometimes requires the use of dopamine infusion (3-10 µg/kg/min). In addition, most anesthesiologists also administer mannitol (12.5-25 g) and furosemide (10-40 mg) after release of the vascular clamps to promote urine production.
SELECTED READINGS

PANCREAS TRANSPLANTATION
The incidence of insulin-dependent diabetes mellitus (IDDM) is approximately 0.5%, indicating that between 1 and 1.5 million people in the US have IDDM. Although subcutaneous injection of insulin is a well-established therapy, it does not result in normal glucose metabolism. Pancreas transplantation is indicated in patients with extremely labile IDDM despite complex insulin regimens and in patients with hypoglycemia unawareness, resulting in poor quality of life. In addition, patients with severe neuropathy, especially autonomic neuropathy, may benefit from pancreas transplantation. Pancreas transplantation should also be considered in patients who already require immunosuppression, most frequently because of a kidney transplant. After successful pancreas transplantation, there is total independence from exogenous insulin administration, and glucose levels should be normal although responses to oral and intravenous glucose administration may be slightly abnormal. Secondary complications will gradually improve, although this may take several years. Importantly, quality of life is significantly improved after pancreas transplantation.

PREOPERATIVE EVALUATION
IDDM results in secondary complications which are the result of microvascular disease and nonenzymatic glycosylation of proteins. The secondary complications are more severe in patients with poor control of IDDM, but eventually all patients will develop secondary complications. Secondary complications include nephropathy, retinopathy, neuropathy, and cardiovascular disease.

Cardiovascular System
The cardiovascular complications of IDDM include ischemic heart disease, idiopathic cardiomyopathy, peripheral vascular disease, and hypertension. Because of the autonomic neuropathy myocardial ischemia and infarction may be silent. Therefore, even in patients without angina, preoperative evaluation should include dobutamine stress echocardiography or adenosine thallium scintigraphy. Coronary angiography may be required in selected patients.

Neuropathy
Abnormal nerve conduction will affect motor, sensory, and autonomic nerves. This results in abnormal cardiovascular and cardiorespiratory reflexes (e.g., orthostatic hypotension), cardiovascular lability (e.g., resting tachycardia), esophageal dysfunction, gastroparesis with delayed gastric emptying, and sudden death.
Renal System
Nephropathy develops in about half the patients with IDDM, and is caused by microvascular changes in the glomeruli and peritubular capillaries.

Anesthetic Management

Monitoring
Hemodynamic monitoring includes electrocardiography (leads II and V5), direct invasive arterial pressure monitoring, and central venous pressure monitoring. Pulse oximetry, multigas analysis, temperature measurement, and peripheral nerve stimulation are routinely performed.

Induction and Maintenance of Anesthesia
Because autonomic dysfunction may result in delayed gastric emptying, rapid frequency induction is commonly used. Many anesthetic agents are acceptable for induction and maintenance of anesthesia, as long as hemodynamic stability is maintained. Autonomic neuropathy of sympathetic nerves may require the use of vasoactive substances.

Metabolic Control
Although there is some evidence that tight glucose control (70-100 mg/dL) may result in better allograft function, commonly the glucose level is kept in the 100-150 mg/dL range. This may require continuous infusion of insulin (0.5-2 U/h) guided by frequent blood glucose determinations. Usually glucose is infused as well (75-100 mL/h of 5% glucose solution) to prevent hypoglycemia. The transplanted pancreas very quickly becomes metabolically active, and insulin should not be required to maintain normoglycemia postoperatively.

Selected Readings
INTRODUCTION
The dream of replacing a diseased human organ with one from a dead person is ancient: legend states that Saints Cosmas and Damien in the fourth century A.D. miraculously transplanted a leg from a dead man. Such a creature would be a chimera, named after the “mingled monster” of Homer’s Iliad. The scientific study of the biology of transplanting tissue dates to the first years of this century, when Little and Tyzzer defined the Laws of Transplantation, paraphrased as: “isografts succeed; allografts are rejected.” The clinical practice of transplantation is governed by these laws. This chapter introduces the immunologic events in transplantation, and in particular the molecular basis of these events, to be supplemented by reviews. Table 1 summarizes our approach, and Table 2 presents some useful terms. A recurrent theme is the “allo” relationship, which describes the relationship between two members of the same species who are not genetically identical. Thus we can describe alloantigens, allografts, and alloantibody.

THE FATE OF ALLOGRAFTS
Allografts are usually rejected in one of three patterns: acute rejection; accelerated and hyperacute rejection; and chronic rejection.

ACUTE REJECTION
Around 5-7 days the tissue begins to manifest signs of two processes: inflammation and specific cell injury. The inflammation is manifested by infiltration with mononuclear cells, accompanied by edema and reduced blood flow; specific destruction of parenchymal and endothelial cells by infiltrating lymphocytes, coupled with decreased perfusion, cause a rapid loss of function. Destruction of blood vessels frequently leads to late infarction of some or all of the tissue.

ACCELERATED AND HYPERACUTE REJECTION
If certain organs, particularly kidneys, are transplanted into a recipient who has high levels of preformed antibodies against donor alloantigens of the graft endothelium, particularly HLA class I (see below) or ABO blood group antigens, hyperacute rejection follows. The antibodies on the endothelium fix complement, which attracts polymorphs, and destroy the endothelium within hours or even minutes. Hyperacute rejection is usually prevented by “crossmatching”, i.e., testing the recipient’s serum for complement-dependent antibodies against donor lymphocytes.15
If the recipient has previously been sensitized against donor antigen, e.g., by pregnancies, transfusions, or previous grafts, but does not have preformed antibodies in the circulation, rejection may occur around day two or three, earlier than typical acute rejection. This accelerated rejection is more vigorous, a reflection of specific immunologic memory for the antigens of the graft. It is mediated by the rapid return of high levels of specific T cells and/or alloantibody directed against the antigens of the graft.

**CHRONIC REJECTION**

An initially successful transplant may gradually lose its function in a slow scarring process. The arteries become obstructed by intimal thickening, and the graft undergoes progressive parenchymal atrophy and interstitial fibrosis. Chronic rejection has been most studied in patients with renal and heart transplants, and can occur months to years after transplantation. In some cases it may be antibody-mediated, but typically no antibody is demonstrable and the pathogenesis is not understood. In heart transplants, the result is a potentially lethal form of diffuse obliteration of the medium and small coronary arteries, sometimes called graft atherosclerosis. In lung transplants scarring of the small bronchioles occurs (bronchiolitis obliterans) whereas in liver transplants the bile ducts are attacked (the vanishing bile duct syndrome).

Rejection is an immune response and the manifestations are attributable to molecules. We will now outline those molecules and how they lead to rejection.
THE PRINCIPAL MOLECULES OF ALLORECOGNITION

Synopsis: Allogenic stimulation results when specific clones of recipient T cells “see” donor major histocompatibility complex (MHC) as nonself, in conditions favorable to triggering. The molecules central to understanding allorecognition are the MHC, T cell receptor (TCR), immunoglobulin (Ig), CD4 and CD8, all of which are members of the immunoglobulin (Ig) superfamily; the adhesion molecules, and the cytokines and their receptors. Allogenic stimulation is thus based on specific antigen recognition, plus a wide variety of permissive nonantigen specific interactions of proteins with complementary sites on other proteins.

First, a reminder. Protein structure is classified as primary, secondary, tertiary, and quaternary. The primary structure is the amino acid sequence, formed by peptide linkages between amino acids (NH-C-C(=O)-NH-C-C(=O)). Secondary structures can be either α-helices or β-pleated sheets, formed by hydrogen bonds between the NH groups in peptide linkages and the oxygens of carboxy (C=O) groups. If these bonds form internally between amino acids four residues apart, an α-helix forms. If H bonds form externally, with a remote portion of the protein, or with a different protein, the adjacent strands of amino acids (β strands) form a β-pleated sheet. Portions with no secondary structure are often termed “loops”. Tertiary structure is the folding and assembly of the sheets, helices, and loops of a polypeptide into a distinct shape. For example, adjacent α-helices can form a bundle, and β-sheets can form barrels. The quaternary structure is the assembly of individual polypeptides into multimers.

Distinct regions (domains) of a protein serve distinct functions. The exons of a gene encoding a protein often echo the domain structure of the protein, with separate exons encoding each domain. Proteins that will be expressed in membranes or secreted often have leader peptides to guide their insertion into membranes. Leader peptides are encoded by leader sequences in the gene.

THE IMMUNOGLOBULIN (IG) SUPERFAMILY

Ig superfamily proteins contain one or more Ig domains. The Ig domain is a polypeptide of about 90 amino acids (molecular weight about 12 kd) typically encoded by one exon. It contains seven β strands, designated A-G, separated by six loops, 1-6 (Fig. 1). The β strands align to form two antiparallel β-pleated sheets, one four-stranded (A, B, E, D) and one three-stranded (C, F, G), connected by a disulfide bond. The β strands confer the structure and the loops mediate many of the functions, especially loops 2, 3 and 6. Many Ig superfamily proteins evolved by tandem duplication of the exon for the Ig domain. They also have other domains, including membrane anchors; intracytoplasmic domains which may have signalling functions; and “sheet and helix” domains, as seen in the MHC proteins.

THE MAJOR HISTOCOMPATIBILITY COMPLEX

The human MHC is the human leukocyte antigen or HLA complex of genes. It spans four million base pairs (bp) on the short arm of chromosome 6 (6p). These genes encode the strong transplantation antigens, the class I and II MHC proteins. We shall examine the structure of these proteins and the organization of the genes.
THE MHC PROTEINS

The MHC class I and II proteins are antigen presenting structures. They bind peptides inside cells and display them on the cell surface for T cells to "read" for signs of intracellular infection. They also play a role in the ontogeny of T cells in the thymus.

Class I is expressed on most cells and samples the peptides in the cytosol, typically for virus infection. Class II has a restricted tissue distribution, confined to specialized antigen presenting cells (APCs) (macrophages and B cells). Class II samples the peptides in the endosomal compartment of antigen presenting cells, looking for proteins taken up by endocytosis, e.g., from extracellular infectious agents. Differences between class I and II are listed in Table 3. They share a similar organization: a pair of Ig domains adjacent to the membrane, plus a pair of "sheet and helix" domains, plus transmembrane and intracytoplasmic portions (Fig. 2).
Table 3. Features of class I and class II MHC

<table>
<thead>
<tr>
<th></th>
<th>Class I</th>
<th>Class II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution</strong></td>
<td>diffuse—all cells</td>
<td>specialized—macrophages and B cells</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>single α chain non-covalently bound to β2-microglobulin</td>
<td>α-β heterodimer</td>
</tr>
<tr>
<td><strong>Size of Peptide Presented</strong></td>
<td>8 or 9 a.a.</td>
<td>13-25 a.a.</td>
</tr>
<tr>
<td><strong>Source of Peptide</strong></td>
<td>cytosol</td>
<td>endosomes</td>
</tr>
<tr>
<td><strong>Important T Cell Co-Receptors</strong></td>
<td>CD4 (on helper T lymphocytes)</td>
<td>CD8 (on cytotoxic T lymphocytes)</td>
</tr>
<tr>
<td><strong>Important Assembly Factors</strong></td>
<td>LMPs, TAPs, chaperone proteins</td>
<td>invariant chain</td>
</tr>
</tbody>
</table>

Fig. 2. The structure of MHC class I and II molecules are compared. The class I molecule includes the β2-microglobulin protein (labelled β2, shown in gray). The class II molecule has the same pattern, but is formed by a dimer of an α and β chain. The domain in the α (α3) chain adjacent to the membrane is similar to β2-microglobulin. C = C terminal. Arrow shows the loop 3 region, which is the site for CD8 interaction with class I and possibly CD4 with class II (Reproduced with permission from: Sigurdardottir S, Borsch C, Gustafsson K et al. J Immunol 1992; 148:968-973.)
THE MHC “Sheet and Helix” Domain in Class I and II Structures

The sheet and helix domains form the peptide binding groove, which is central to the whole immune response. The first half of each sheet and helix domain (about 45 amino acids) has four β strands—A, B, C, D—folded antiparallel to form a β sheet. The remainder of the domain forms a long interrupted α-helix. Two sheet and helix domains pair face-to-face: the β-pleated sheets align to form a single eight-strand β-pleated sheet which serves as the floor of the groove, and the α-helices form the walls.

The class I groove accommodates short peptides of about nine amino acids, and the class II groove accommodates longer peptides—13-25 amino acids. A concerted effort is underway to solve the rules which govern the occupation of the groove by peptides.

The structures of both class I and class II are known. Class I and II molecules are organized differently (Fig. 2). The class I has a long α chain, with two sheet and helix domains (α1 and α2), one typical Ig domain (α3), a membrane anchor, and an intracytoplasmic domain. The structure is completed by β2-microglobulin, a single Ig domain, which interacts with the α3 domain. An important region of class I is loop 3 of the α3 domain which interacts with CD8.

The class II molecule is assembled from a pair of nonidentical class II proteins, an α chain and a β chain. Each has a sheet and helix domain, an Ig domain, a membrane anchor, and an intracytoplasmic domain. The two sheet and helix domains (α1 and β1) form the peptide binding groove. The loop 3 region of the second domain of class II b chain forms the site of interaction with CD4.

THE MHC Genes

The DNA of the human MHC can be divided into four regions: class II and III regions, each 10⁶ bp; the class I region, 1.5 x 10⁶ bp; and the class Ib region, 0.5 x 10⁶ bp. The organization of the HLA genes is shown in Figure 3.

A class I gene has eight exons: a leader sequence, two exons encoding sheet and helix domains (α1 and α2), the exon for the Ig domain (α3), an exon for the transmembrane region, and three short exons for the cytoplasmic domain. Most of the polymorphism is in selected sites of exons 2 and 3. While about eight class I genes are expressed in HLA, the most important for clinical transplantation are A and B. The β2-microglobulin gene is encoded separately on chromosome 15.

A class II gene has five or six exons: a leader sequence; exon 2 encoding the sheet-and-helix domain; exon 3 encoding the Ig domain; and two or three exons encoding the membrane anchor and cytoplasmic domain, for a total of five or six exons. Most of the class II polymorphism is in selected sites in exon 2. The expressed class II genes, in order, are two DP genes (DPB1, DPA1), one DN gene (DNA), one DO gene (DOB), two DQ genes (DQB1, DQA1); a variable number (1-3) of DRB genes, depending on the haplotype; and DRA. For transplantation the important class II genes are the DRA and B.

MHC Polymorphism

MHC class I and II genes are highly polymorphic, in selected sites, namely the bases that encode amino acids which determine the shape of the peptide binding groove. These sites create pockets and reactive groups which interact with the
amino acid side chains of peptides. Polymorphism of these sites may be generated by exchange of short DNA sequences between closely related genes ("interallelic segmental exchange"). Segmental DNA exchange preserves a "cassette" of amino acids which work together to create a binding site. The MHC polymorphisms have been developed over tens of millions of years.

CONTROL OF GROOVE OCCUPANCY: ANTIGEN PROCESSING AND PRESENTATION

Class I MHC molecules present peptides from endogenous proteins and class II MHC molecules present peptides from exogenous proteins, with exceptions. This difference stems from the routes of intracellular trafficking for class I and II after they are synthesized in the endoplasmic reticulum (ER).

Newly synthesized class I heavy chains fold and assemble noncovalently with P2-microglobulin and peptide in the ER. The binding of peptides stabilizes the
heavy chain—β₂-microglobulin complex for transport via the Golgi apparatus to the cell surface, guided by chaperone proteins.37,38

Newly synthesized class II molecules in the ER cannot bind peptide because a portion of the invariant chain occupies the peptide groove.39 Invariant chain guides the class II from the ER through the Golgi apparatus to an acidic compartment of endosomes.40-42 Proteins taken into the cell by endocytosis enter the acidic endosome and are broken down by proteases. Invariant chain protecting the class II groove is also degraded in the endosome,43 freeing the groove to bind peptide. Peptides 13-25 amino acids in length occupy the grooves of class II molecules.44 Class II molecules may “select” peptides by protecting fragments of larger proteins from degradation.44 A larger peptide bound in the class II groove could hang out the ends and the exposed ends may be “trimmed”.45 After peptide binding, class II is stable and is transported to the cell surface.

Endocytic vesicles from the cell surface sample the external environment and also receive self membrane-bound molecules. Thus DR1 molecules often contain peptides from self MHC class I and II.48,49

In B cells antigen binds to the B cell receptor and is internalized into the endosome. Such antigenic proteins are broken down into peptides, bound by class II, and exported to the cell surface to permit T cells to help the B cell to make an antibody response (see below). In addition, the endosome may receive cytosol-derived peptides transported via chaperones of the heat shock protein 70 (hsp70) family.47,48 This enables class II to present some endogenously derived peptides.34

PROTEASOMES AND PEPTIDE TRANSPORTERS

To permit cytosolic peptides to be displayed by class I molecules, proteins from the cytosol must be broken down to short peptides, and the peptides must have access to class I grooves in the ER. This requires mechanisms to degrade proteins and to transport the peptides into the ER. Peptides are generated by proteasomes, large cytoplasmic complexes containing protease activities. Genes for two proteasome components are located in the class II region, although their function is to assist class I products.49-51 The proteasome genes are termed LMP2 and LMP7 (large multifunctional protease genes). They are polymorphic subunits of the proteasome complex which lyses cytoplasmic proteins.52-54 The transporters (called TAPs or transporters associated with antigen processing) are TAP1 and TAP2.51,55-64 The transporters are located in the membrane of the ER. Polymorphisms occur in the TAP genes but the importance of these is unknown.

Thus cytosolic proteins are digested into peptides by proteasomes, access the ER via transporters, and engage the groove. The LMP and TAP genes, like the class I heavy chain and the class II genes, are upregulated by IFN-γ.49

ANTIGEN RECOGNITION MOLECULES

A specialized Ig domain—the variable or V domain—is found at the N terminal of Ig light (L) and heavy (H) chains, all TCR chains, and CD4, CD8, and ICAM-1 molecules. In V domains, loop 3 between strand C and strand D forms two more β strands C’ and C”, and joins β strands C, F, and G to form a five-stranded β-sheet (C’, C, C, F, G) (Fig. 1).
In antigen recognition receptors (TCR, immunoglobulins), the V domains are highly variable or "hypervariable" to permit specific recognition of many different antigens. The variability is confined to loops 2, 3, and 6 (Fig. 1). These loops form the "complementarity determining regions" or CDRs: loop 2 forms CDR1, loop 3 CDR2 and loop 6 CDR3. The CDRs form the combining sites in antibodies and T cell receptors that recognize specific antigens. The six CDRs determine the antigenic specificity.

**Immunoglobulin, B-Cell Receptors and Antibody**

An antibody molecule is formed by two L chains and two H chains. Each L or H chain has a variable region, V_{H} or V_{L}, which is a single V domain, and a constant region, C_{H} or C_{L}. The L chain constant region is one Ig domain. The C_{H} region consists of three or four Ig domains. The V regions of the L and H chains pair to form the antigen binding site: the three CDRs of V_{H}, plus the three CDRs of V_{L}. H chains are of five types, designated by the Greek letter for the Ig class in which they are found: α, IgA; γ, IgG; µ, IgM; δ, IgD, and ε, IgE. In transplantation the most relevant Ig classes are IgM and IgG.

B lymphocytes and their progeny, plasma cells, make immunoglobulin. Immunoglobulin can serve as the antigen receptor or can be released into the circulation. Each clone of B cells expresses only one type of L chain (lambda or kappa) with one type of VL region. It can make only V_{H}, but can associate this with different C_{H} regions to form the antigen binding site: the three CDRs of V_{H}, plus the three CDRs of V_{L}. The V regions of H chains are of five types, designated by the Greek letter for the Ig class in which they are found: α, IgA; γ, IgG; µ, IgM; δ, IgD, and ε, IgE. In transplantation the most relevant Ig classes are IgM and IgG.

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**T-Cell Receptor (TCR)**

The TCR (Fig. 4) is a dimer of nonidentical α and β chains. There is a second TCR, which is a dimer of γ and δ chains, but most allore cognition can be attributed to αβ receptors. Each TCR α or β chain resembles an Ig light chain, having V and C regions, with the addition of a membrane anchor and intracytoplasmic region. The TCR V region is believed to be similar to the Ig V region. The V domain is hypervariable in loops 2, 3, and 6, forming CDR1, CDR2, and CDR3 in each V region of the dimer. The V_{α} and V_{β} regions dimerize face to face with their CDR3s adjacent in the center and their CDR1 and 2 on the outsides. Despite the fact that the TCR structure is not solved, inferential evidence confirms this model. The γδ receptor may be similar.

**How the TCR Engages MHC**

It is likely that all six CDRs of the TCR engage the upper surface of the MHC. The outer regions of the TCR (CDRs 1 and 2) engage the α-helices of the MHC, and the central region (the CDR3s) engages the peptide. One model is that the TCR-α chain CDRs engage the α-helix of the α1 domain of class I or class II. The
TCR-β chain engages the other α-helix—either the α2 domain of class I or the β1 domain of class II. The CDR3 region is the most variable of the CDRs in the T-cell receptor. This fits well with the notion that the CDR3s have to bind to the antigenic peptide, whereas the CDR1 and 2 must engage the α-helices, which are much less variable. The affinity with which soluble TCR binds MHC in solution is surprisingly weak, much less than the affinity of antibody for antigen.\(^6\) This puzzle is not explained.

**CD4 and CD8**

CD4 and CD8 are termed co-receptors because they bind to the same MHC molecule as does the TCR, and are often important for TCR triggering. The CD4 molecule is a chain of four Ig domains plus a membrane anchor and an intracellular
portion. The CD4 first and second domains form a rigid rod because the last β strand of the first domain (strand G) is elongated to become the first β strand of the second domain (strand A). The N terminal domain is of the V type. The third and fourth domains repeat this arrangement to give a second rod, hinged to the first. The two N terminal domains engage the β chain of MHC class II (Fig. 5). The CD4-class II β2 domain interaction may be species specific.

The CD8 molecule is a dimer, similar to TCR. The CDR loops of the V domains of CD8 engage the class I MHC molecule in the α3 domain. CD8 may be either an αβ or αα dimer; the functions of these dimers may differ. The CD8-class I interaction is species specific, which could be relevant in xenotransplants.

**Fig. 5.** T cell receptor (TCR) engagement with the MHC. The TCR engages the upper surface of the MHC molecule. The co-receptors, CD4 for class II and CD8 for class I, also bind to the MHC, often triggering the TCR. The two N terminal domains of the CD4 engage the MHC class II. The structure of the TCR-MHC complex has never been solved. (Garboczi DN, Ghosh P, Utz U et al. Nature 1996; 384:134-141)
DIVERSITY, VARIABILITY AND POLYMORPHISM

The MHC, TCR, and immunoglobulin products must exist in many forms to mediate specific antigen recognition. This requires diversity in the corresponding genes, but the demands on MHC products are very different from those on TCRs and antibodies. MHC products are antigen presenting structures which must exist in many forms in the human population but few forms in any one individual. Thus MHC genes encode the proteins without random generation of diversity, but with enormous numbers of alleles in the population.

Antigen receptors (Ig and TCR) generate diversity randomly from a high number of genes encoding V regions of the L and H chains. These Ig genes rearrange in B cell precursors to randomly generate great diversity in selected sites, the CDRs. Thus, unlike the MHC alleles, the TCR and antibody genes combine germ line diversity with massive randomly generated somatic diversity to give each person an enormous repertoire of V region specificities by which antibody or TCRs can engage antigen. The potential repertoires of Ig and TCR chains is estimated at $10^6$ to $10^9$ specificities each.

Each Ag recognition structure involves combining two different chains (heavy chain with light chains in the Ig molecule, and $\alpha$ with $\beta$, or $\gamma$ with $\delta$ in the TCR). The potential diversity created by combining such diverse molecules increases beyond $10^{10}$ for antibody and beyond $10^{15-18}$ for TCR $\alpha\beta$ and TCR $\gamma\delta$.

In the case of MHC genes, the polymorphism is mainly confined to the bases encoding the amino acids lining the groove. In the TCR and Ig genes, the diversity is mostly confined to the regions encoding CDRs.

WHAT IS ALLORECOGNITION?

When T cells of a recipient encounter allogeneic MHC, in the context of appropriate additional signals, stimulation of some of the recipient T-cell clones occurs. How allorecognition occurs in vivo is not clear. Small numbers of amino acid differences in the donor MHC can lead to strong responses. This could be because (1) they alter groove shape and thus determine peptide occupation of the groove; (2) they change the shape of the upper surface of the native molecule and change the interaction with the TCR; or (3) they make MHC peptides antigenic.

The donor MHC differences can be presented by either a direct or indirect pathway of presentation. “Direct” refers to recipient T cells recognizing donor MHC molecules on donor antigen presenting cells. Direct recognition could reflect recognition of $\alpha$-helix differences affecting the contact sites for TCRs on the $\alpha$-helices, or differences in the peptides in the groove, or $\gamma$-chains.

“Indirect” presentation of donor MHC requires recipient antigen presenting cells with peptides of donor MHC molecules in their grooves. Recent evidence has emphasized the importance of the indirect pathway, particularly since immunity and tolerance can be induced by peptide alone.

THE POTENTIAL IMPORTANCE OF PEPTIDES OF DONOR MHC ANTIGENS

Peptides from MHC class I proteins are prominent among peptides occupying the class I groove and peptides of class I and II and invariant chain are prominent in the class II groove of DR1. This has given rise to the possibility that a
major component of — across an MHC difference is due to recognition of MHC peptides in the donor (direct) or host (indirect) MHC grooves.

Indirect presentation of allogeneic donor MHC peptides in self MHC class II grooves (and possibly in class I grooves) by host antigen presenting cell (APC) must involve recognition of differences in amino acid sequences. Indirect presentation is a distinct possibility for triggering CD4 T cells, and could generate "help" for both T cell and antibody responses as well as inflammation akin to "delayed type hypersensitivity". However, graft injury by cytotoxic T cells must involve direct recognition.

T-CELL RECOGNITION AND TRIGGERING8,10,11

Synopsis: Engagement of the TCR and CD4 or CD8 activates protein tyrosine kinases (TKs) associated with the intracytoplasmic portions of the receptor. TKs trigger second messengers and initiate several signalling pathways which eventually alter proteins which regulate the transcription of genes for cytokines and cytokine receptors. This locks the T cell into activation. Signals provided by additional membrane receptors such as CD28 also play a key role ("second signals").

THE NATURE OF TCR TRIGGERING

The binding of sufficient TCRs to MHC molecules is a necessary condition for T cell activation by antigen. The signal requires the CD3 complex, which includes γ, δ, ε, and the long ζ chains.89 How does TCR binding to MHC alter CD3? This problem is generally explained by one of two mechanisms:

1. Conformational change: engagement of the V regions alters remote parts of the TCR, which in turn alters the CD3 complex; or
2. Crosslinking: the TCR complexes are brought together by engaging antigen and activate one another. Dimerization of class II molecules may serve to bring TCRs together to aid triggering. This would imply that class II recognition may proceed through a complex of two TCRs and two CD4s.

Crosslinking is a common mechanism of triggering of receptors in general. Class I may be able to form multimers,90 and the dimeric nature of CD8 and of class II suggest that crosslinking could occur.79 Nevertheless, TCR-mediated T cell activation in vivo may reflect molecular changes triggered by the assembly of the TCR-CD3-CD4 or CD8 complex, in which the CD4 or CD8 molecules play key roles, particularly if the affinity of the TCR for the MHC is low.91

The CD3 complex is the transducer which tells the interior of the cell that the TCR has engaged MHC. The ζ chains interact directly with the tyrosine kinases. Meanwhile CD4 (or CD8) engage the MHC, and assembly of the complex brings a series of tyrosine kinases together.

THE KEY ROLE OF TYROSINE KINASES

The CD3-TCR complex is associated with at least three TKs: ZAP, p59μ, and p50κ. CD4 and CD8 are associated with another protein tyrosine kinase, p56Δ. TKs phosphorylate the tyrosine residues in the CD3 molecule ζ chain, in key transduction molecules, and in one another. The functions of p56Δ and p59μ...
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have been shown in knockout mice to be nonoverlapping: p59^{fyn} knockouts have defective TCR signalling and p56^{lck} have defective thymocyte development. The tyrosine kinase p50^{csk} may be particularly involved in negative signalling (tolerizing) the T cell when the TCR is signalled. TKs activate many signalling pathways, including:

1. Ras: the tyrosine kinases can activate the Ras pathway through recently discovered intermediate proteins such as Shc and GRB2; activation of Ras then triggers a cascade which can activate enzymes such as mitogen activated protein kinase (MAP kinase) and eventually impact on cell division.

2. PLC-γ, which lyses the membrane phospholipid phosphatidyl inositol bisphosphate to yield IP₃ and diacylglycerol (DAG). DAG activates protein kinase C (PKC) and inositol trisphosphate (IP₃) binds to receptors on the ER to release stored calcium and raise intracytosolic Ca²⁺ levels. The high Ca²⁺ is then sustained by increased calcium entry through channels in the plasma membrane to maintain high cytosolic Ca²⁺ concentrations.

3. Phosphatidylinositol-3-kinase and several others.

Each of these pathways has multiple consequences leading to expression of many genes, blast transformation, mitosis, and expression of effector functions. The calcium-dependent pathway is critical for T-cell activation and important in transplantation. High intracellular calcium activates calcium-regulated enzymes, particularly the enzyme calcineurin (CN). This is a calcium- and calmodulin-dependent serine phosphatase. It activates transcription factors for some key cytokines, particular members of the nuclear “factor of activated T cells” or NF•AT family. CN is the target for some of the most important immunosuppressive agents, cyclosporine and tacrolimus (FK506).

Within minutes, mRNA is transcribed from the “immediate” genes, which do not require new protein synthesis. Some of these are transcription factors. The newly synthesized transcription factors, plus the newly activated factors, now activate a second set of genes. The mRNAs and products for IL-2, IFN-γ, and other cytokines and certain cytokine receptors then appear.

**COSTIMULATION (“SIGNAL 2”)**

When the naive T cell encounters alloantigen, it requires other signals before proceeding with activation, in keeping with the classic two-signal model of lymphocyte activation. Signal 1 is the allogeneic MHC antigen, which must be at a high density to trigger a primary T-cell response. High antigen expression may be one reason why antigen presenting cells (dendritic cells and macrophages) are required. “Signal 2” is the nonantigen signal provided by antigen presenting cells.

(A classic belief in immunology is that when T cells engage antigen without appropriate second signals, anergy results. This renders the identity of the second signals crucial for transplantation and immunosuppression. If we could block them, we might induce anergy.)

“Signal 2” may involve certain adhesion molecules of the Ig superfamily, notably B7-1 and B7-2 (also called B70) on the APC, engaging CD28 on the T
CD28 activates systems in the T cell which synergize with the signals from the T-cell receptor. CD28 amplifies and prolongs signal 1, increasing IL-2 transcription and prolonging the half life of IL-2 mRNA. In CD28 knockout mice, T-cell triggering can still occur, indicating that other systems can compensate. Other signals from the antigen presenting cell, which could contribute to signalling, include other adhesion molecule ligand receptor pairs on the APC and T cell respectively (ICAM-1-LFA-1 and LFA-3-CD2), and cytokines such as IL-1 and IL-6 produced by the antigen presenting cell.

Stimulation of the primary T-cell response may require all of these, in a “conversation” between T cells and APCs initiated by high density of the allogeneic class II molecules on the APCs in the context of cytokines and adhesion molecules. The signals from the triggered CD4 T cells then activate the APCs to increase the signals to the T cell in a cascade of reciprocal activation.

One of the key sites for regulating signal 2 may be expression of CD40 ligand. CD45 is a tyrosine phosphatase on the surface of all marrow-derived cells whose function may be to keep the key tyrosine in tyrosine kinases (lek and fyn) dephosphorylated and ready to participate in triggering.

**Details of Signal Transduction and T-Cell Activation: Control of Cytokine Expression**

PLC-γ1, activated by tyrosine phosphorylation, lysed membrane phosphatidyl inositol bisphosphate (PIP2), releasing DAG and IP3. DAG activates PKC which is also activated through other pathways, including calcium flux. PKC activation leads to the transcription of several genes which encode transcription factors such as fos and jun which form the complex called AP-1, composed of the Jun and Fos proteins.

IP3 binds to receptors on the endoplasmic reticulum which release calcium into the cytosol. The high cytosolic calcium is then sustained by changes in membrane transport. The high calcium activates calcium-dependent enzymes, one of which is CN. CN activates cytosolic factors called NF-AT, which is free to translocate from the cytosol to the nucleus. When cytoplasmic and nuclear factors assemble to form the full NF-AT complex, transcription of IL-2 mRNA begins. While the NF-AT sites account for the majority of inducible IL-2 expression, it is likely that the NF-κB site and the octamer site are also critical. The characteristic behavior of the IL-2 gene requires the interaction of multiple transcription factors binding to these sites.

Similar events occur with other cytokine genes, although less is known about them. The result is a wave of transcription of cytokine mRNAs. Note that this is the “second wave” of protein synthesis, the first being the nuclear factors which control the cytokine promoters. In this sense the cytokines are “early”, not “immediate” genes.

Naive CD4 T cells make predominantly IL-2 in their first encounter with antigen, whereas previously stimulated or memory T cells make other cytokines. IL-2 engages its receptor, and other cytokines engage through their receptors, giving waves of receptor triggering and signal transduction. The cell becomes committed to activation, differentiation, mitosis, and clonal expansion. Effector functions
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emerge such as cytotoxicity in CD8 cells. Eventually the molecules associated with memory and recirculation, such as the "very late antigens" or VLA molecules, appear.

**Cytokines and Their Receptors**

The term "cytokine" includes the interleukins, interferons, and colony stimulating factors of the hematopoietic and host defense system. They are protein mediators which signal cells through specific membrane receptors. Cytokines and their receptors are related in structure and function to protein hormones and their receptors. Cytokines have certain characteristics:

1. Short half-life: cytokine mRNAs and cytokines themselves have short half-lives to permit fine regulation.
2. Relatively small size: the typical cytokine gene is about 4-5 kb in length, with about four exons. Numerous AT sequences at its 3' end confer a short half life on the mRNA. The protein is typically a polypeptide chain of about 10-20 kD, often glycosylated and/or multimerized to a higher molecular weight.
3. α-helical structure: many cytokines are folded into a bundle of four to six α-helices, sometimes with very short β strands. Exceptions include TNF-α, a sandwich or "jelly roll" of antiparallel β strands, and TGF-β, which has both α-helices and β-pleated sheets.
4. Multimer formation is common: IFN-γ and TGF-β are dimers, and TNF-α is a trimer.
5. Cytokines are generally not stored but are synthesized and secreted when needed. They are not usually expressed as membrane proteins, but some have membrane-bound variants, e.g., TNF-α and IL-1.
6. The main control of cytokine production is transcriptional, although post-transcriptional control is known, e.g., for TNF-α.

Cytokines often act in concert with other cytokines: interactions (synergy, competition, and antagonism) are common. Cytokines are pleiotropic (i.e., have many effects) and redundant (i.e., have overlapping effects). Cytokines commonly induce other cytokines in a cascade. Self-amplifying circuits are common to facilitate rapid potent responses. The potency of the cytokine response is impressive as is well known to the clinician who observes the cytokine release syndrome after OKT3 treatment (see below).

Some cytokines are produced in normal tissues at low levels and affect growth, development, and homeostasis, e.g., the maturation of T and B lymphocytes. But their most characteristic effects are in inflammation and host response to injury or infection.

"Knockout mice" are providing important insights into the roles of cytokines and their receptors. In knockout mice, both copies of the target gene have been mutated to prevent expression. Such strategies may underestimate the importance of the deleted structure because the deletion forces the embryo to use other cytokines to develop, thereby maximizing apparent redundancy. Moreover,
the laboratory mouse, protected from many of the usual pathogens of its species, tolerates immune defects which would be more serious in the natural environment. Surprises arise in knockouts: for example the IL-2 and IL-10 knockouts, as well as some TCR knockouts, get inflammatory bowel disease for unknown reasons.\textsuperscript{124,125}

Cytokine receptors are typically multimers of different transmembrane proteins, one or more which have an external ligand-binding domain, and an intracytoplasmic signalling domain. One or more chains may bind the cytokine with high affinity, but the multimer is required for internalization and/or signalling. Cytokine receptors are classified into families on the basis of their external, ligand binding domain.\textsuperscript{126-128}

1. The hemopoietins, e.g., IL-2R\(_{\beta}\) chain, use a 200 kd external domain with four conserved cysteines and one tryptophan residue at the N terminal, and aromatic residues (Trp-Ser-X-Trp-Ser) at the C terminal. A few receptors in this group have typical Ig domains in their extracellular regions.
2. The interferon and IL-10 receptors, e.g., IFN-\(\gamma\)R, have two external domains distantly related to Ig domains, with characteristic conserved cysteines.
3. The TNF receptor and its relatives have an external domain with cysteine-rich repeats.\textsuperscript{128}
4. IL-8 and its relatives have a “seven pass” membrane receptor associated with G proteins, similar to many endocrine receptors.

Unlike the cytokines, which are often predominantly \(\alpha\)-helical, the external ligand binding domain of a hematopoietin or interferon receptor is often two \(\beta\)-pleated sheets. A second chain of the receptor may or may not actually engage the cytokine; in the IL-2 receptor it does, but in the IFN-\(\gamma\) receptor the binding site is formed by the single receptor protein with the second receptor component presumably playing other roles. Binding of the cytokine to the external domain of the receptor may alter the cytoplasmic domain, triggering second messengers usually through a kinase, usually a protein tyrosine kinase or less commonly a serine/threonine kinase. The signalling systems are similar to those already described: PTks activate PLC-\(\gamma\), PI-3 kinase and other second messengers with downstream activation of serine-threonine kinases, e.g., PKC and release of intracellular calcium.

The final effect is often on transcription factors, but other events are common, such as direct effects on membrane receptors or cytoplasmic effector mechanisms.

Signal transduction, through the IFN-\(\gamma\) receptor,\textsuperscript{109} is a useful example of a cytokine system which we can watch in operation in transplant rejection. IFN-\(\gamma\) engages the IFN-\(\gamma\)R and activates two tyrosine kinases, JAK1 and JAK2, which phosphorylate a factor called STAT 91. This induces transcription of selected genes by moving to the nucleus and engaging specific sites in their promoters. We will expand on some features of the IFN-\(\gamma\) response later as an example of cytokine signal transduction. The TNF receptor acts through a sphingomyelin pathway to induce NF-kB to be released from its cytoplasmic binding protein (IkB) to enter the nucleus and bind to specific DNA regulatory sites.\textsuperscript{118}
From the above, the passage of signals from hematopoietin and interferon receptors to the interior of the cell involves the regulation of tyrosine phosphorylation. The cytoplasmic regions of many membrane receptors for protein hormones have intrinsic tyrosine kinase activity, but cytokine receptors are associated with separate tyrosine kinases (like JAKs which associated with the IFNL-γ-R). Engagement of the receptor by its ligand activates the tyrosine kinase activity, which results in phosphorylation of one or more key tyrosine residues in the cytoplasmic region of the receptor. This phosphorylated tyrosine can then be recognized by other proteins via specific regions in those proteins called “src homology-2” or SH2 domains. The sequence “ligand-receptor-tyrosine kinase activation-tyrosine phosphorylation—recognition and binding of a second messenger via its SH2 domain activation of second messenger by tyrosine phosphorylation—is probably a common pattern for linking membrane receptors to second messengers like STAT proteins.

Several cytokine receptors, including IL-2R, apparently utilize a signal transduction pathway which involves the activation and phosphorylation of an enzyme called the “Target of Rapamycin” or TOR. TOR in turn activates p70 S6 kinase. The role of TOR was discovered because the immunosuppressive drug rapamycin acts at this point. The role of TOR kinase is probably crucial in the initiation of cell division by cytokines. TOR acts to increase the translation of existing mRNAs for proteins which control the cell cycle.

**SPECIFIC IMMUNE RESPONSES OF T CELLS AND B CELLS**

*Synopsis:* Specific lymphocyte activation leads to cell cycling (clonal expansion), T cell/B cell-antigen presenting cell interactions, altered cell traffic, and altered expression of many genes in the transplanted organ and elsewhere in the host. The lymphocyte population changes. Many lymphocyte activation events may actually occur within the graft, as opposed to the lymphoid organs. Three lines of lymphocyte differentiation lead to effector mechanisms, which require massive clonal expansion to become quantitatively important:

1. The delayed type hypersensitivity response, principally engineered by cytokines from CD4 T cells;
2. The B-cell antibody response, dependent on CD4 T cell help;
3. The cytotoxic T-cell response by CD8 cells.

Activated CD4 cells influence other cells through two mechanisms: the production of cytokines, which interact through their receptors to signal the target cell, and direct interaction through their TCRs and adhesion and signalling molecules. Direct interactions must involve the same MHC plus peptide for which the CD4 T cell is primed. In direct interactions, the release of cytokines is directional, focused on the target by the TCR and the adhesion molecules. Activated CD4 cells help CD8 cells to become cytotoxic and B cells to make antibody and activate macrophages and endothelial cells to mediate delayed type hypersensitivity.
DIVISION OF LABOR AMONG CD4 CELLS: “TH1” AND “TH2” CYTOKINES

The primary function of CD4 T cells is to produce cytokines, which they do more efficiently than CD8 cells. Naive CD4 T cells produce primarily IL-2, with increasing amounts of assorted other cytokines. With prolonged stimulation, e.g., in cloning experiments in vitro and under certain conditions in vivo, CD4 T cells cease production of some cytokines and increase production of others in characteristic patterns: a “TH1” pattern or “TH2” pattern. The TH1 pattern of cytokine production is IFN-γ, lymphotoxin, and IL-2. The TH2 pattern consists of IL-4, IL-5, IL-6, and IL-10 (Table 4). These are called the TH1 and TH2 cytokines respectively. CD4 T cells can be found which produce exclusively TH1 or TH2 cytokines and are called TH1 and TH2 T cells or subsets. But typically the intermediate forms are much more frequent.

No cytokine or surface antigen constitutes an exclusive marker for any CD4 phenotype; for example, IL-10 can be produced by CD4+ T cells of the TH2 characteristics but also by many TH1 cells in human and by many non T cells. IFN-γ is a “TH1 cytokine”, but most of it is made by other T cells (CD8 T cells and CD4 T cells not fitting the TH1 definition) or by NK cells. We prefer to reserve the term TH1 and TH2 “subsets” for circumstances where we know that discreet populations, rather than a continuum, can be shown to exist. Under most circumstances TH1 and TH2 cytokines are not made by CD4 T cells which fulfill the criteria for TH1 and TH2 subsets.

TH2 cytokines are more important in helping B cells. In vitro the activation of resting B cells to proliferate and differentiate requires cytokines, particularly of the TH2 type, e.g., IL-4, IL-5. In addition, IL-10 enhances in vitro viability of B cells and upregulates MHC class II expression on resting small dense B cells from mouse spleens.

TH1 cytokines can enhance or suppress B cell responses, according to the relative amounts of IL-2 and IFN-γ produced. IL-2 in large amounts enhances differentiation, proliferation, and Ig production. IFN-γ in low concentrations

Table 4. Some cytokine phenotypes of mouse CD4 T-cell clones

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<th>Cytokine Phenotype</th>
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<th>TH2</th>
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<td>GM-CSF</td>
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<tr>
<td>TNF-α</td>
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<td>IL-3</td>
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<td>TH2 cytokines:</td>
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<td>IFN-γ</td>
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<td>Lymphotoxin</td>
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enhances certain antibody responses but in high amounts suppresses both proliferation and Ig secretion and can be cytotoxic to activated B cells. TH2 cytokines favor IgE and IgG1 responses (through IL-4), whereas TH1 cytokines in mice induce IgG2a.

The generation of CD8+ cytotoxic T cells is enhanced by both TH1 and TH2 cytokines. IL-2, IFN-γ, IL-4, and IL-5 all enhance the generation of CTLs although IL-2 is most effective.

TH1 cytokines are important mediators of delayed type hypersensitivity (DTH) (see below). TH1 and TH2 cytokines cross-regulate. TH1 and TH2 cytokines tend to be mutually inhibitory regardless of what cell is producing them. IFN-γ inhibits the proliferation of TH2 clones and IL-10 suppresses both cytokine production and proliferation of TH1 clones. IL-10 inhibits IFN-γ production by TH1 clones by 90% and inhibits production of TH1 cytokines by CTL clones and LGL. IL-10 acts at the level of antigen presenting cells and their relatives such as skin Langerhans cells.

T cells from IL-2 knockout mice have disturbed cytokine production in vitro, overproducing IL-4, IL-6, and IL-10. In vivo, such mice have increased serum levels of IgG1 and IgE due to increased IL-4 production. For IL-10 knockouts the results are less clearcut.

REVISING THE CONCEPT OF “SUPPRESSOR T CELLS”

Mixing nonresponding and responding populations of T cells can shut off the responders. This “contagious” unresponsiveness used to be attributed to a special class of “suppressor T cells”, typically carrying CD8 markers, but it is now clear that antigen-specific T cells with unique suppressor function cannot be isolated. Suppression is a cell population phenomenon, not attributable to unique specialized cell class. All cytokines have both positive and negative effects, and the cells which produce them cannot be assigned a uniquely positive or negative function except in relationship to one specific set of circumstances and one specific target system. For example, TH2 cytokines such as IL-4 can suppress DTH responses but help IgE responses. Thus T cells producing IL-4 can have many simultaneous functions, positive and negative, depending on where the IL-4 is received. So suppression by IL-4 is really a characteristic of the cell that receives IL-4, not the cell that produces it. Similarly, cells producing TGF-β are negative regulators in some types of inflammation and positive in others.

Thus negative regulation or suppression can often be explained without postulating the existence of specialized suppressor cells. In clinical transplantation, where negative regulation is vital to success, the agenda has shifted from suppressor T cells to a detailed analysis of the role of particular molecules in negative regulation of graft injury and inflammation, such as TH2 cytokines and TGF-β.

THE ALLOANTIBODY RESPONSE AGAINST MHC ANTIGENS

B-cell activation normally takes place in germinal centers (GC) of draining lymph nodes or spleen, but may occur in the graft infiltrate of a transplant. The surface Ig of the B cell, slg, engages the polymorphic regions of the donor MHC,
particularly the α-helices, in the native, nondenatured, unprocessed form. The MHC antigen is probably shed from donor cells. This leads to B cell triggering and internalization of the antigen. The mechanisms of signalling through slg involves a receptor complex on the B cell similar to the CD3 complex on T cells. The result is that a signal for B cell triggering is delivered, activating intracellular pathways which include the calcium-dependent pathway.

To recruit antigen-specific T cell help, B cells must present peptides of allogeneic MHC antigen in the groove of its class II antigens. To accomplish this, the allogeneic MHC antigen bound by slg is endocytosed, through proteins around the receptor termed α and β, and presented as peptides in the class II groove of the B cell. Host B cells thus present peptides of donor MHC to host CD4 T cells. Antigen presentation by a B cell is crucial for the T-cell response. T cell-B cell interactions are weak unless the T cell recognizes its cognate antigen on the B cell. The CD4 T cells may initially be sensitized by antigen on host or donor dendritic cells because antigen specific B cells are uncommon in the early stages of the response before they are triggered and undergo clonal expansion. CD4 T cells, B cells, and DCs presumably interact in multi-cell complexes.

T cell-B cell engagement involves a variety of adhesion and signalling interactions, including CD4 with class II, CD40 ligand with CD40, LFA1 with ICAM-1, and CD2 with LFA3, CD5 with CD72, etc. Several cytokines are also transmitted from the CD4 cell to the B cell and B-cell signalling molecules such as CD40 help to trigger the T cell. The expression of adhesion molecules, cytokines, and cytokine receptors increases. The signals to the B cell from the T-helper determine whether the B cell will progress towards antibody production and memory, or toward anergy/apoptosis (programmed suicide). Apoptosis is regulated by the gene bcl-2 in lymphocytes; mice with knockouts of bcl-2 gene have spontaneous suicide of their lymphoid tissues and lymphocytes.

If the signals are correct, the B cell undergoes massive clonal expansion and differentiation. Ig, initially expressed on the B cell membrane, can now be released in large quantities as circulating antibody against MHC and other alloantigens.

**What Sites on the MHC Does Alloantibody Recognize?**

Alloantibody recognizes the “nonself” sites in the α-helix and the ends of the β-pleated sheets that are due to the effect of polymorphic amino acids. The most abundant and important Ig class produced is IgG, which has two antigen binding sites. Each IgG can engage only one site in the MHC molecule. The other binding site of the alloantibody can engage the same region of another MHC molecule. The alloantibody usually binds to the side of an MHC sheet and helix domain or to the top of one α-helix, not across the groove like the TCR. However, one IgG molecule will not fix complement efficiently: an adjacent IgG molecule is needed. The best way of assuring that such IgG complexes will be assembled is to have multiple clones responding to different sites in the mismatched molecule. This is usually the case with clinically important anti-MHC responses: they are polyclonal and react with several sites on the MHC molecule.
Does the peptide in the MHC groove influence antibody binding to the MHC? Perhaps, because the peptide may alter the shape of the domain, as well as possibly directly contacting the antibody in a few cases. Alloantibodies specific for the MHC allele plus a specific peptide are known and would escape detection in our usual antibody screening programs. Alloantibody which required a specific peptide would usually react with too few MHC molecules to be quantitatively important. It is conceivable that alloantibody recognizing abundant tissue specific peptides in MHC alleles could act as tissue specific alloantibodies in rejection, e.g., anti-endothelial antibodies. This could help to resolve the old problem of tissue specific alloantibodies such as anti-endothelial antibodies.

**Cytotoxic CD8 Response**

Whether the naive CD8 cell requires an APC for its primary stimulation is less well established than for the CD4 cell. The presence of the CD4 cytokines and possibly direct contact from CD4 have been suggested to be necessary for the CD8 cell to be triggered. However, CD8 cells can also be directly triggered without CD4 cells at times, as shown in CD4 deficient or class II deficient mice.

With time and clonal expansion, the CD8 cell acquires the ability to be cytotoxic for target cells. Cytotoxicity is direct lysis of target cells in suspension with the targets undergoing programmed cell death (apoptosis). Functional cytolytic ability correlates with the expression of serine esterases (granzymes) and perforins. Although both are sequestered in cytoplasmic granules, perforins and granzymes are regulated differently. Another mechanism of target cell lysis is the interaction of a TNF-like molecule on the T cell (Fas ligand) with a TNF-receptor-like molecule on the target (Fas). Cytolytic ability also requires adhesion molecule interaction between the cytotoxic T cell and the target cell.

**The Possible Role of Natural Killer (NK) Cells in Allorecognition**

NK cells can lyse cells with little or no class I, apparently being inhibited by expression of class I. This may reflect recognition of the class I groove by an NK receptor. Little is known about such receptors, and the role of NK cells in transplantation is uncertain.

**Organization of Inflammation**

The inflammation in the graft is analogous in some respects to the delayed type hypersensitivity reaction (DTH), exemplified by the classic skin reaction to tuberculin. DTH is an in vivo phenomenon with no single in vitro correlate. It is manifest histologically as a heterogeneous nonspecific inflammation with edema, fibrin accumulation, T-cell infiltration (both specific and nonspecific), B cells, numerous macrophages, and lesser numbers of other leukocytes, and endothelial changes. The key events in DTH are cytokine production (especially TNF-α and β, IFN-γ and IL-1), altered expression and function of adhesion molecules, and nonspecific activation of many bone marrow-derived cells, particularly macrophages. Although usually ascribed to CD4+ T cells, DTH reactions mediated by CD8 T cells have been described. The result is graft inflammation.
THE ADHESION MOLECULES

These sets of molecules, which are involved in all levels of the immune response and inflammation, are classified into three groups: the Ig superfamily; the integrins; and the selectins.

ADHESION MOLECULES OF THE Ig SUPERFAMILY

The principal members are ICAM-1, ICAM-2, VCAM, CD2, CD58, CD28, CTLA4, B7-1, B7-2. These tend to be involved in signalling as well as adhesion. Their expression is increased by pro-inflammatory TH1 cytokines. Ig superfamily members generally interact with other Ig superfamily members or with integrins. ICAM-1 is a chain of five Ig domains with a membrane anchor and an intracytoplasmic region. Its N terminal domain binds the integrin LFA1. The N terminal V domain of ICAM-1 uses the CDR2-like loop to interact with LFA-1.168 The interactions of CD2-LFA3; CD28-B7, as well as Ig domain interactions with integrins, may follow these principles. Detailed modelling of the interactions involving the Ig superfamily will permit the design of better monoclonal antibodies or other antagonists.

INTEGRINS

Integrins are heterodimers of an α chain and a β chain. The integrins are classified on the basis of the β chain they employ as β1, β2, or β3 integrins. Each β chain can potentially be combined with many different α chains. β1 integrins are important markers of memory and recirculation in T cells (the VLA group). β2 integrins are important in leukocyte adherence reactions (LFA-1, Mac-1).169 Both β1 and β2 integrins are activation-dependent with low avidity in the unactivated state, but high avidity following T-cell activation. Integrins are also associated with diapedesis and intracellular signalling.

SELECTINS

The selectins are large molecules with three characteristics: lectins (sugar residues with the ability to bind to sugars on other molecules), epidermal growth factor-like motifs, and short consensus repeats (2-9). Each also possesses intracytoplasmic domains. The name selectin helps us to remember these features: S (short consensus repeats), e (epidermal growth factor-motif), and lectins.

There are three members, named for the cells that express them. E (endothelial)-selectin, is induced by IL-1 and TNF. Its ligand is L(leukocyte)-selectin, which is important for both endothelial binding during inflammation and as a recirculation receptor. L-selectin also binds to P(platelet)-selectin, which is stored in granules of platelets and endothelial cells and is released in response to clotting cascade products.

Selectin interactions are weak under flow conditions and serve as first step adhesion receptors. By slowing leukocyte passage, they expose the leukocytes to the local environment and other endothelial surface molecules. Selectins are involved in all types of tissue injury and may be important mediators of reperfusion injury in transplanted organs. Antibody against P-selectin has been used to ameliorate reperfusion injury of lungs, presumably by inhibiting the interaction of neutrophils with injured endothelium.170
THE ROLES OF ADHESION REACTIONS
The leukocyte interacts with endothelium through interactions between the selectins. The result is loose binding permitting the leukocyte to roll along the endothelium. This permits the integrins and Ig superfamily members to interact, which causes tight binding and flattening. This will occur only in areas where the endothelium has been activated by injury, infection or immune activity to increase the expression and activity of the adhesion molecules.

THE ACCUMULATION OF THE INTERSTITIAL INFILTRATE IN A TRANSPLANT
The first entry of T lymphocytes into the allograft probably occurs by a combination of nonspecific and specific interactions with endothelial cells. Antigen nonspecific cells interact poorly with nonactivated endothelium but may be attracted by endothelium activated by nonimmune injury from the transplant donor, the surgery, or the preservation. Antigen specific T cells probably interact with donor APC in the organ or in the host for their primary stimulation and begin the process of activating the endothelium. Sensitized lymphocytes, primed by antigen plus APC in lymphoid organs, or from a previous encounter, can then interact with the allogeneic endothelium both to infiltrate the tissue and eventually to damage the endothelium.

The T-cell response may be initiated in the central lymphoid organs such as spleen and lymphoid tissues with homing to the graft through a combination of antigen specific and adhesion molecule interactions. Inflammation is characterized by changes in vascular flow and permeability and the influx of leukocytes to the area of injury. Classic signs of inflammation—redness, edema, heat, and loss of function—are present in an acutely rejecting graft. The immune response in the interstitial areas of the graft alters the endothelium of the graft to recruit inflammatory cells. Once there, some leukocytes undergo proliferation within the graft, particularly the clones of lymphocytes which encounter their cognate antigens. Others, such as macrophages, undergo activation and immobilization in response to the products of activated T cells.

ENDOTHELIAL CELLS (EC)
Far from being inert lining cells, EC can act as antigen presenting cells and can respond to many stimuli. EC respond to cytokines in a variety of ways, ranging from selective induction of increased MHC class II and class I expression to a generalized increase in the function and expression of many adhesion molecules to generalized activation and even proliferation. They interact with leukocytes through their adhesion molecules, including E-selectin, P-selectin, ICAM-1, ICAM-2 and VCAM-1. IFN-γ, IL-1 and TNF all induce expression of adhesion molecules. Other regulated responses include changes in hemostasis, vascular tone and permeability. Hemostasis is altered in the direction of promoting thrombosis and fibrin formation through synthesis of thromboplastin and suppression of thrombomodulin/protein C. Platelet activating factor (PAF) has been demonstrated in the EC plasma membranes and may act locally on adhering leukocytes.

Vascular tone is regulated by EC through local release of endothelin, a potent vasoconstrictor, and nitric oxide (NO), an endothelium-derived relaxing factor.
Nitric oxide synthase (NOS) exists in two principal forms: a calcium-activated constitutive form in endothelium and in many other cell types and a cytokine inducible form in macrophages. Other influences include eicosanoids such as the vasodilator prostacyclin (PGI₂) or the vasoconstrictor thromboxane. Cytokines affect vasomotion: IL-1 can induce the synthesis of endothelin by EC, and TNF induces both endothelin and NO production in bovine aortic EC. It is likely that the balance between these two forces contributes to the complex vasmotor changes such as arterial vasoconstriction and capillary leak in acute rejection. IL-1 and TNF alter vascular permeability in vivo, probably through intermediate actions on neutrophils, and could thus play a role in the edema characteristic of acute rejection.

In addition to NO, PGI₂, thromboxanes, and endothelin, EC respond to the inflammatory cytokines IL-1 and TNF by producing other soluble factors. These include IL-1α, IL-6, PAF, various chemokines (see below), M-, G- and GM-CSF. IL-1α activity appears predominantly associated with the EC plasma membrane and may provide co-stimulation to bound T cells during antigen activation. IL-6, particularly in the presence of IL-4, is abundantly secreted by EC. PAF, like IL-1α, may be predominantly membrane bound and its effects may be very localized.

**The Chemokines**

Chemokines are recently described as a family of cytokines, 8-10 kD in size, with activity in inflammation and tissue repair, such as attracting inflammatory cells. Members include IL-8, Groα, monocyte chemotactic protein (MCP), and RANTES. The cDNA for these cytokines have been recognized by their characteristic gene structure, typical signal sequences in the 5’ region, AT rich sequences in their 3’ untranslated regions, and rapidly inducible mRNA expression. All the chemokines have cysteine residues which form disulphide bridges. These cytokines appear to play a key role in inflammation and immune responses by their chemotactic activities and their ability to attract and activate neutrophils, monocytes, T cells, eosinophils and basophils (Table 5). Antigen specific T cells activated by APC express new chemokine receptors, which are 7-pass receptors which activate G proteins. These antigen-activated T cells, now capable of directional migration into an inflammatory site in response to chemokines released in the inflamed site, reenter the circulation. T-cell infiltration into the challenged area probably involves a process of sequential endothelial adhesion and then release of T cells, followed by adherence to extracellular matrix via integrin molecules. One current hypothesis is that MIP-1α, MIP-1β, or RANTES participate in attracting the appropriate T cell subsets to an inflammatory site.

IL-8 and Gro-α are chemoattractant for neutrophils and contribute to extravasation of neutrophils. Neutrophils can produce several polypeptides mediators of inflammation, including IL-1, IL-6, IL-8 and TNF. At the site of injury neutrophils promote tissue damage by release of lysosomal enzymes and superoxide anions. Lung reperfusion injury and neutrophil infiltration can be prevented experimentally by a monoclonal antibody (mAb) against IL-8, raising the possibility that organ preservation as well as immune activity could be improved through manipulation of chemokines.
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CHANGES IN THE TARGET TISSUE

In an inflamed tissue, the expression of many surface molecules increases, usually because cytokines increase the transcription of the genes. The example of IFN-γ triggering the transcription of the MHC class I and II genes in vivo is the best known, but many adhesion molecules can also be induced on endothelium, inflammatory cells, and parenchymal cells. We shall outline the features of the induction of class I and II MHC molecules by IFN-γ.

THE TRANSCRIPTIONAL REGULATION OF MHC GENES

The level of MHC expression determines the immunogenicity of tissues and their sensitivity to immune injury, and some increased MHC expression is invariably seen in acute T cell-mediated rejection. The expression of MHC proteins in tissues is primarily regulated by transcriptional control.

MHC genes behave as “housekeeping genes” (as opposed to tissue specific genes), which are either expressed or expressible in most tissues, but to varying degrees. This implies that the chromatin structure of their regulatory regions is available for transcription factors in many tissues.

In the normal mammal, constitutive class I expression is widespread but highly variable between cell types. A component of IFN-γ-induced expression is common even in normal hosts. Constitutive class II expression is confined to B cells. The class II expression in dendritic cells and some macrophages in normal individuals may reflect low levels of cytokines such as IFN-γ, IL-4, and GM-CSF. Class II expression found in some normal epithelia probably also reflects cytokine induction.

MHC PROMOTERS

The level of MHC expression is closely related to the steady state mRNA levels and probably reflects the activity of the promoter in regulating transcription. The class I and II promoters are highly conserved.

The characteristic DNA sequence in the class I promoter is a class I regulatory element (CRE) at about -160 to -200 bp from the start site of transcription, overlapping an interferon consensus sequence (ICS) at about -140 to -160 bp. The CRE is a series of overlapping palindromic sequences which are sites of binding...
of transcriptional regulatory proteins and are necessary for the tissue specific basal and induced expression of class I. Protein binding to the CRE seems to correlate with constitutive class I expression. The ICS probably binds proteins which are regulated by IFN-α/β and IFN-γ and acts by increasing transcription in concert with the CRE. TNF-α also acts on the CRE, probably through NF-κB proteins.

The class II promoter contains a conserved region at about -60 to -100 bp which contains sequences termed the X box, Y box, and a spacer between them. The X and Y boxes are occupied by proteins in the basal state and probably are the elements giving class II genes their characteristic patterns of regulation in the basal and cytokine induced state, but other elements participate. The key regulation of class II genes is the class II transactivator, or CIITA.

**NORMAL AND INDUCED IFN-γ PRODUCTION AND REGULATION**

IFN-γ is produced by T cells (CD4, CD8) and NK cells. IFN-γ production is an important event in rejection, with both adverse and favorable effects. IFN-γ-mediated MHC induction is probably necessary but not sufficient for rejection, and IFN-γ can induce accelerated rejection. IFN-γ is produced by the specifically triggered T cells and is also capable of triggering its own release, probably from NK cells with the appearance of large granular lymphocytes (LGL). Thus the LGLs may serve as an amplifier to increase the release of IFN-γ.

**IFN-γ RECEPTOR TRIGGERING**

Two IFN-γ receptors bind the IFN-γ homodimer, each engaging the N terminal of one unit and the C terminal of the other. Receptor crosslinking leads to membrane-to-cytoplasm signal transduction via mechanisms involving the large intracytoplasmic domain of the receptor. The mechanism involves a protein kinase: the receptor becomes phosphorylated, and one tyrosine in the intracytoplasmic portion of the receptor has been shown to be essential to the biological activity of the receptor. The receptor has additional subunits, encoded on chromosomes 21 and chromosome 16 in the human. Tyrosine kinases (JAK1 and JAK2) then phosphorylate the cytoplasmic form of a transcription factor, interferon stimulated gene factor 3, in particular, the p91 component, now called STAT-1. This then moves into the nucleus to activate transcription of genes with IFN-γ activated sites. Some of these induced mRNAs encode products which are transcription factors.

The details of the pathway from the IFN-γ receptor to MHC promoters remain to be elucidated; it is unclear why MHC expression tends to be induced later than some other genes, e.g., 24-48 hours after IFN-γ administration. It is likely that MHC induction requires the synthesis of IFN-induced transcription factors such as IRF-1. In the case of class I induction, the signal transduction pathway used by IFN-γ seems to require some of the same steps as are used by IFN-α/β. These proteins probably affect the ICS. In the case of class II, the new protein induced by IFN-γ is CIITA.
TARGET INJURY

CANDIDATE MECHANISMS OF SPECIFIC DONOR CELL INJURY IN REJECTION

The hallmark of acute T-cell mediated rejection is injury to the endothelial and parenchymal cells, initially reversible, but eventually becoming irreversible and proceeding to infarction. Inflammation is probably necessary but not sufficient for rejection injury. The parenchymal injury is usually conceptualized as apoptosis of individual parenchymal cells triggered by cytotoxic T cells. Many cytokines such as TNF-α are expressed in rejecting or inflamed grafts, but no single cytokine has been shown to mediate rejection injury. Understanding of what constitutes rejection injury should begin with the pathology, not with immunologic theory.

THE PATHOLOGY OF ACUTE REJECTION

International collaborations have classified the histologic lesions which correlate with rejection. Classifications are all based on the concept that donor cell injury, not the inflammatory infiltrate or interstitial edema, defines rejection. Thus tubulitis in kidney transplants, myocyte necrosis in heart transplants, injury to the biliary epithelium of liver transplants, and injury to the epithelium of small airways in lung transplants, constitute rejection. In general, areas of high MHC class I and II expression, either basal or inducible, are important targets of acute rejection.

Tubulitis in renal transplants refers to invasion by lymphocytes which cross the basement membrane and attack the basolateral membrane of the epithelial cells, where MHC products are expressed (Fig. 6). Bile ductule invasion, damage to small airway epithelium, and myocyte necrosis probably involve analogous mechanisms. The lymphocytes are believed to be T cells expressing cytotoxic molecules, but more details on the cells in these lesions are needed.

![Fig. 6. Acute tubulitis. Lymphocytes infiltrate through the basement membrane and recognize alloantigens expressed on the MHC of graft epithelial cells and mediate cell death via apoptosis or cell lysis.](image-url)
The endothelium of small arteries and arterioles in all types of grafts is damaged in the lesion known as intimal arteritis or endothelialitis. (Such lesions are often missed in biopsies: for example, endomyocardial biopsies of rejecting heart transplants are relatively poor at sampling arteries.) Lymphocytes adhere to the endothelium, infiltrate beneath it and lift up the endothelial cells. The result is increased resistance, perhaps due to loss of endothelial regulation of vasomotion, increased coagulation, and eventual loss of perfusion and downstream ischemia.

The candidate mediators of specific cell injury include cytokines, Fas and granule contents (serine esterases and perforins), both concentrated on the target cell by receptor directed exocytosis, and in some cases cytotoxic alloantibody. Serine esterases are expressed in the infiltrate of rejecting grafts. At least some of the injured graft cells probably die by apoptosis. Numerous cytokines are found in the infiltrate of rejecting grafts or in the serum, but the roles of these mediators are not established. Some may cause injury, but some may reflect the response to injured tissue. Both CD4 and CD8 T cells are present in rejection and neither has an exclusive role.

There are nonspecific as well as alloantigen-specific lymphocytes in the cellular infiltrate. Macrophages are abundant within rejecting grafts and may play a role in the immune injury. Macrophages make a wealth of cytokines, growth factors, eicosanoids, enzymes, procoagulant activities, NO, etc, and may contribute to the parenchymal and endothelial cell injury and dysfunction in vascularized grafts. But the majority of early injury is probably due to specific T cells.

**The Role of Antibody in Acute Rejection**

Alloantibody can play a major role in acute transplant rejection, especially in the increasing population of recipients sensitized to MHC antigens. EC are important targets for alloantibody. The sequence of events in antibody-mediated rejection seems to involve endothelial dysfunction and injury, via complement and neutrophils, followed by vasospasm, ischemic injury, fibrin and/or platelet deposition, and infarction or hemorrhage.

Hyperacute rejection is predominantly a problem in renal transplantation, mediated by preformed antibodies against HLA class I molecules or by antibodies such as ABO blood group antigens. A population of antibodies against poorly defined endothelial antigens of arteries ("anti-endothelial antibodies") also mediates hyperacute and accelerated rejection. Anti-class II antibodies rarely mediate hyperacute rejection. A positive B-cell crossmatch is frequently due to antibodies which are not class II specific. For example, antibodies against B cells are often autoantibodies. Low levels of anti-class I can also produce a positive B-cell crossmatch with a negative T cell crossmatch because B cells are relatively rich in class I. Thus a positive B-cell crossmatch may have several explanations.

Successful immunosuppressive strategies usually suppress primary alloantibody as well as T cell responses, probably by suspending help from CD4 T cells, but do little to preformed antibody and may have difficulty suppressing secondary antibody responses.
Anti-class I-mediated rejection of kidney transplants can be recognized clinically. Typically a transplant into a presensitized patient with a negative crossmatch functions initially, then suddenly loses function after 1-7 days. The kidney may rapidly develop acute tubular necrosis secondary to severe decrease of perfusion. The pathology shows evidence of endothelial injury in the microcirculation, rather than tubulitis or endothelialitis. Neutrophils may be present. The demonstration of antibody against donor class I can aid the diagnosis. OKT3 can sometimes suppress this rejection by abrogating T-cell help. Anti-class I-mediated acute rejection of the heart may also occur.

HOST AND GRAFT ADAPTATION

Synopsis: Despite immunosuppression, transplantation could not be successful if adaptive changes favoring prolonged graft survival did not occur in both the host and the graft. The adaptive changes in the graft may reflect the loss of the donor bone marrow-derived cells, with the loss of “signal 2”. The antigen specific adaptive changes in the host are dependent on the continuous presence of the antigens of the graft — and on immunosuppressive therapy, in many or most patients. The host probably develops a state of partial peripheral tolerance.

HOST ADAPTATION

The encounter of the immune system with antigen can result in a positive response, a negative response (“tolerance”), or no response (“neglect”), depending on the circumstances in which the antigen is presented. Tolerance is defined as a state of antigen-specific unresponsiveness induced by exposure to antigen, typically under conditions of immaturity, injury, or drug therapy. The ability to induce tolerance is vital for self and nonself discrimination and to randomly generate potentially autoreactive cells. T cell tolerance is classified by location: central versus peripheral.

CENTRAL TOLERANCE

The principal central mechanism of tolerance in the thymus during T-cell ontogeny is clonal deletion by apoptosis. Intrathymic injections of antigen can induce tolerance in rats, but these approaches have not yet been successful in primates. Central tolerance is believed to have little role in transplantation although microchimerism with donor cells could play a role centrally. In general, chimerism can induce tolerance only in significant levels, and microchimerism does not correlate with true tolerance.

PERIPHERAL TOLERANCE

Successful transplantation involves a degree of peripheral tolerance. Studies of transgenic mice expressing foreign MHC antigens in peripheral tissues have recently been particularly helpful for understanding peripheral tolerance (reviewed in ref. 206). These and other models suggest several possible mechanisms:

First, in some models, clonal expansion then clonal deletion occurs, causing peripheral tolerance. This is particularly true for responses to ‘superantigens’,
which delete previously expanded clones as an outcome of powerful immune responses probably by programmed cell death. Lack of co-stimulatory signals (IL-1, adhesion molecules) may promote peripheral clonal deletion. Overall, however, peripheral clonal deletion is not a prominent mechanism.

Clonal anergy, i.e., paralysis without deletion, is demonstrable in some circumstances. In some MHC class I transgenic mice, tolerance is the result of anergy and is dependent on the continuous presence of Ag and the lack of IL-2. Exogenous IL-2 reverses the state of anergy. Some patients receiving long-term immunosuppression with functioning allografts simulate this state. In some models of MHC class II transgenic mice, T cells exhibit low reactivity against class II in vitro, with no in vivo pathology, a form of "neglect". IFN-γ may abrogate some tolerant states. Cytokines of the TH2 type, e.g., IL-10, may suppress IL-2 and IFN-γ expression, but it is difficult to imagine long-term high levels of cytokine production as a mechanism for maintaining tolerance. Clinical immunosuppressive treatment, particularly with cyclosporine and steroid, may also act in this way, selectively reducing IL-2 and IFN-γ production.

A variety of other mechanisms could be important:

1. Down-regulation of TCRs and co-receptors (CD4 or CD8);
2. "Veto cells" (these are T cells which inactivate T cells which try to recognize them);
3. Antigen-specific T cells actively maintaining unresponsiveness, especially CD4 T cells. CD4 T cells producing TH2 cytokines could decrease the production of TH1 cytokines from other lymphocytes in a "contagious" fashion;
4. Anti-idiotypes. Idiotypes are antigen combining sites, either of TCRs or antibodies, and anti-idiotypes are antibodies which are directed against them. The extensive literature on anti-idiotype antibodies and idiotype-specific regulatory T cells has not led to examples of negative regulation unequivocally mediated by an idiotype/anti-idiotype interaction. There is evidence for the role of anti-idiotypes in turning off anti-HLA antibody responses.

**ADAPTIVE CHANGES IN THE GRAFT**

With time, if the graft survives, the inflammation subsides, and the induced expression of adhesion molecules and MHC antigens in the graft returns toward normal. There is a progressive loss of the donor antigen presenting cells, replaced by the recipient cells. Thus both direct antigen presentation by donor cells and indirect presentation by host cells subside. Injuries, including ischemic and reperfusion injury, rejection, and viral infection, can promote inflammatory changes and sustain the immune process. The changes of inflammation and those of tissue repair in response to injury overlap. Immunologic and nonimmunologic injury can both therefore lead to a common pathway of chronic inflammation which manifests itself in sub-acute or chronic rejection. Thus injury may sustain the host APC and antigen expression burden of the graft, sustaining immunologic activity and preventing the stabilization of the host graft relationship.
MICROCHIMERISM

The transfer of tissue from a donor to a recipient transfers some bone marrow-derived cells, some of which are stem cells. The donor bone marrow-derived cells can persist and establish bone marrow microchimerism, i.e., permanent persistence of small numbers of bone marrow derived stem cells of donor type, presumably due to establishment of a few donor stem cells. This would link transplantation-induced peripheral tolerance with classic neonatal tolerance in mice, which is probably a chimeric state. Microchimerism after blood transfusion may explain the well known blood transfusion effect and why matching of HLA antigens between the blood donor and recipient helps to establish the hyporesponsive state. Some long-term transplant recipients have evidence of microchimerism, even decades after the transplant. Persistent donor cells could be the result or the cause of host hyporesponsiveness. Microchimerism in long-term survivors could lead to central tolerance and clonal deletion by colonization of the host thymus by donor stem cells.

Implantation of allogeneic tissues in the thymus before allografting is an experimental strategy for inducing some central tolerance in rodents. It remains a challenge to demonstrate that this technique works in large animals and man.

CHRONIC REJECTION

This is a process whereby a successful graft begins to develop a slow deterioration in function, usually with nonspecific features which do not easily make for diagnosis. Each organ has unique features, but certain themes recur, including:

1. Thickening of the intima of arteries and arterioles due to smooth muscle cell invasion and proliferation;
2. A degree of parenchymal atrophy and interstitial fibrosis which may or may not represent ischemia.

The organ specific features are:

1. Heart: severe diffuse concentric coronary artery disease extending into small vessels.
2. Kidney: some cases have proteinuria and a variable glomerular lesion termed “transplant glomerulopathy”. Hypertension is frequent.
3. Lung: obliterative bronchiolitis dominates the picture with marked narrowing of the respiratory bronchiole.
4. Liver: destruction of the bile ductules (vanishing bile ducts) may be the dominant lesion.

Chronic rejection often follows acute rejection, and some observers believe that acute rejection, incompletely reversed, is the harbinger of chronic rejection. Despite its nonspecific features, chronic rejection may result from a specific immune response. Earlier beliefs that alloantibody causes chronic rejection have now been tempered by the realization that relatively few cases have evidence of donor-specific antibody. The immune mechanisms appear to be additive with other factors related to the age, acute injury, hypertension, etc. The final common pathway may have elements in common with other chronic diseases or aging.
REFERENCES

26. Connolly JM, Hansen TH, Ingold AL et al. Recognition by CD8 on cytotoxic T lymphocytes is ablated by several substitutions in the class I a3 domain: CD8 and the T-cell receptor recognize the same class I molecule. Proc Natl Acad Sci USA 1990; 87:2137-2141.


43. Chicz RM, Urban RG, Lane WS et al. Predominantly naturally processed peptides bound to HLA-DR1 are derived from MHC-related molecules and are heterogeneous in size. Nature 1992; 358:764-768.


64. Monaco JJ, McDevitt HO. Identification of a fourth class of proteins linked to the murine major histocompatibility complex. Proc Natl Acad Sci USA 1982; 79:3003-3005.
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189. La Rosa FG, Talmage DW. Major histocompatibility complex antigen expression on parenchymal cells of thyroid allografts is not by itself sufficient to induce rejection. Transplantation 1990; 49:603-609.


Infections in Transplant Recipients

Valentina Stosor

INTRODUCTION

Over the past two decades, significant advances were made in the management of infections occurring after transplantation. Even so, infection remains a leading complication of organ transplantation, and the prevention and management of such infections are an important element of care in transplant recipients. Infections are associated with allograft rejection, and therefore, a key to a successful transplantation is the prevention, diagnosis, and treatment of infectious complications.

In this chapter, the most important infectious disease issues that affect different organ-transplant populations are reviewed, including the prophylaxis of infection after transplantation (Table 1).

PRETRANSPLANTATION INFECTIOUS DISEASES EVALUATION

Prevention is, above all, the most important approach to infection in transplant recipients. This begins with a rigorous evaluation to identify previous infections and potential active infectious processes in all candidates before transplantation.

A complete history and physical examination is performed during the pretransplantation screening evaluation. Information regarding past infections is sought, such as childhood illnesses (chickenpox, rubella, measles, and infectious mononucleosis), recurrent sino-pulmonary infections, viral hepatitis, and sexually transmitted diseases. Allergies to antimicrobial agents are documented. Past immunization records are reviewed, and immunizations are administered or updated, if necessary. These vaccines include the inactivated polio, tetanus-diphtheria, influenza, pneumococcal, varicella (if nonimmune), hepatitis B, and hepatitis A (if nonimmune), Haemophilus influenzae type B (pediatric patients), and measles-mumps-rubella (pediatric patients). Dietary habits are obtained, including drinking water source and consumption of raw or undercooked meat, unpasteurized milk products, and seafood.

Epidemiological exposures are identified through social, sexual, recreational, occupational, and pet and wild animal exposure histories. Certain workplace settings, such as healthcare facilities, prisons, and homeless shelters, increase the risk for exposure to infectious agents, especially tuberculosis. Residence or travel exposure to certain agents can identify candidates that are at risk for reactivation of infection after transplantation. Examples of these pathogens include: Histoplasma capsulatum (Ohio and Mississippi river valleys), Coccidiodes immitis (Southwestern...
Table 1. Prophylaxis of infection in transplant recipients

<table>
<thead>
<tr>
<th>Type of Anti-Infective Prophylaxis</th>
<th>Allograft Type</th>
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<tbody>
<tr>
<td></td>
<td>Liver</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Oral selective bowel decontamination</td>
</tr>
<tr>
<td>Fungi</td>
<td>Oral selective bowel decontamination</td>
</tr>
<tr>
<td></td>
<td>High risk only: consider fluconazole</td>
</tr>
<tr>
<td>PCP</td>
<td></td>
</tr>
<tr>
<td>Toxoplasma</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>For CMV D+/R: oral GCV for three months</td>
</tr>
<tr>
<td>HSV</td>
<td></td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td></td>
</tr>
</tbody>
</table>
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Pre-transplantation infection testing (Table 2) includes a complete blood count (CBC) with differential, blood chemistries, urinalysis and urine culture, a tuberculin skin test (PPD), and a chest radiograph (CXR). Serologic evaluation for toxoplasmosis (particularly for heart transplant), syphilis (RPR or VDRL), cytomegalovirus (CMV), herpes simplex viruses (HSV), and varicella zoster virus (VZV) are routinely obtained. Additional screening for viruses includes serologic testing for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). All candidates with the appropriate endemic exposures should have serologies for Strongyloides stercoralis and the endemic mycoses, H. capsulatum and C. immitis. In lung transplant candidates, especially those with cystic fibrosis, sputum cultures are important for the detection of colonization of the respiratory tract by pathogens such as Aspergillus species and Burkholderia cepacia. These organisms pose a risk for the development of significant infections after transplantation as the recipient becomes immunosuppressed. CT imaging of the paranasal sinuses should be considered for patients with cystic fibrosis and others with a history of recurrent or symptomatic sinus infections.

**Timing of Post-Transplantation Infections**

Susceptibility of a host to the development of an infection after transplantation varies according to specific environmental circumstances, surgical factors, and the level of immunosuppression at any given time. Transplant-related infections are categorized according to the relative risk periods that correspond to the evolution of immune deficiencies and technical factors that render the recipient vulnerable to infection. While it is important to entertain infectious etiologies within this context, the transplant physician should consider a broader differential diagnosis of infection in the transplant recipient, as atypical pathogens and presentations of disease can occur in these hosts throughout the post-transplant course.
First Month Post-Transplantation

At this time the degree of immunosuppression is not high enough to render patients susceptible to opportunistic pathogens; therefore, the most frequent infections are related to surgical and nosocomial complications such as bacterial and candidal wound infections, urinary tract infections, nosocomial pneumonias, and central venous catheter-associated bacteremias and fungemias. When dealing with infected recipients in this time period, consideration is given to the type of organ transplanted and the anatomical details of the surgical intervention, as infection is often related to such factors. Patients may have infection related to prolonged stays in the intensive care unit including Clostridium difficile-associated diarrhea or infections with antimicrobial-resistant bacteria such as vancomycin-resistant enterococci. HSV is the only common viral pathogen of this period, manifesting as stomatitis in HSV-seropositive patients.

The Early Post-Transplant Period

This period extends from the second to the sixth month after transplantation. During this time, the level of immunosuppression is most intense. Patients are at high risk of developing serious opportunistic infections including CMV infection and disease, Pneumocystis carinii pneumonitis (PCP), invasive aspergillosis, disseminated toxoplasmosis, dermatomal and disseminated VZV infection, and certain bacterial infections such as listeriosis. Pre-existing infectious agents that can also reactivate during this period include Mycobacterium tuberculosis and the endemic mycoses.

The Late Post-Transplant Period

Beyond six months after transplantation, recipients that have not had allograft rejection episodes requiring increase immunosuppression are at risk for the usual community-acquired infections; however, certain opportunistic infections can still manifest at this late time. Examples include tuberculosis, cryptococcosis, nocardiosis, and herpes zoster. Recurrence of HBV and HCV infections is also seen. The time frame outlined above is “set back” whenever allograft rejection is treated and immunosuppression is augmented with anti-CD3 monoclonal antibodies (OKT3), anti-lymphocyte globulin (ALG), steroid boluses, or radiation. Recipients with chronic allograft rejection also remain at higher risk for the development of opportunistic infections.

Bacterial Infections

Bacterial infections occur in 33-68% of liver transplants, 21-30% of heart transplants, 54% lung transplants, 35% of pancreas transplants, and 47% of kidney transplants. The types of infections encountered and the bacterial etiologies differ depending on the transplanted organ and the surgical technique used. Below, bacterial infections are reviewed in the context of the transplanted organ.
Liver and Intestinal Transplantation

Overview
The most common bacterial infections following liver transplantation are intra-abdominal and surgical wound infections. Cholangitis, abscesses, and intra-vascular device-related bacteremias are other frequent complications. The main risk factors associated with intra-abdominal infections are prolonged surgical time, high transfusion requirements during surgery, re-operations, early rejection, re-transplantation, and CMV infection.

The type of biliary anastomosis influences the risk of post-transplant infections. The choledochojunostomy is associated with less infection risk because the native sphincter of Oddi is maintained. The presence of a Roux-en-y choledocojejunostomy, required in patients with abnormalities of the extra-hepatic biliary system, is associated with a higher incidence of post-operative cholangitis as well as infection following liver biopsy and cholangiography procedures after transplant. This is likely caused by reflux of intestinal contents and microbial flora into the biliary system.

The specific bacterial etiologies of infection after liver transplantation depend on the gastrointestinal flora of the recipients. In the absence of exposure to antimicrobial agents, the enteric gram-negative bacilli such as coliforms, the Enterobacteriaceae, and occasionally, Pseudomonas species, are the predominant organisms causing infection, along with enterococci, staphylococci, and the anaerobes. Infections with vancomycin-resistant enterococci (VRE) are a significant problem in some transplant centers.

Clinical Presentation
Recipients with wound infections or intra-abdominal abscesses may present with any of the following: fever, abdominal pain, wound dehiscence, and purulent wound drainage. On physical examination, pain may be elicited by palpation, and guarding and rebound may be present. Laboratory abnormalities may include leukocytosis with a left shift. However, the absence of leukocytosis or fever does not exclude the presence of infection in the transplant recipient. The definitive diagnosis is achieved by imaging studies such as computerized tomography (CT), ultrasound (US), or magnetic resonance imaging (MRI).

Cholangitis usually manifests with fever and right upper quadrant pain, with tenderness and rebound on palpation of the abdomen. Hyperbilirubinemia, elevated transaminases and alkaline phosphatase levels, as well as leukocytosis, may be found on laboratory testing.

Treatment
Fluid collections are aspirated and cultured. Optimal treatment requires specific pathogen identification by culture of purulent secretions, fluid collections, and blood and antimicrobial susceptibility testing. If an abscess is confirmed, drainage, whether surgical or CT/US-guided, is necessary to achieve an appropriate therapeutic response. Antimicrobial regimens are tailored to the specific pathogen isolated, and empiric coverage for known colonizing flora is appropriate in
seriously ill patients while awaiting final culture results. The use of cephalosporins, fluoroquinolones, carbapenems and beta-lactam+beta-lactamase inhibitor combinations are appropriate choices for complicated intra-abdominal and surgical wound infections.

Cholangitis is managed medically with intravenous antibiotics if there is adequate biliary flow. When obstruction of the biliary tree is present, a therapeutic procedure, such as ERCP with dilatation, is performed.

Again, third- and sometimes second-generation cephalosporins, as well as the other antibiotics mentioned above, are reasonable antimicrobial choices depending on the culture results.

**Prevention**

Adequate surgical technique is one of the most important factors that prevent infectious complications. Because of the high morbidity and mortality of gram-negative infections, the eradication of oral and gut flora may be desirable. This is accomplished with the use of oral selective bowel decontamination (OSBD), consisting of nonabsorbable antibiotics that eliminate gram-negative aerobic bacteria and fungi. These regimens spare gram-positive and anaerobic organisms that have an antagonistic effect on the growth of gram-negative pathogens. OSBD is most effective when initiated one week prior to transplant surgery and continued post-operatively for one to three weeks. Whereas the overall incidence of infection with OSBD is not different than without it, there is a substantial decrease in the incidence of gram-negative bacteremias, which carry a high mortality as mentioned above. After OSBD, most infections in patients are secondary to gram-positive organisms. Some centers have noted the emergence of infections caused by resistant gram-positive organisms such as VRE; however, the exact relationship to OSBD is unclear.

Peri-operative prophylaxis with an extended-spectrum cephalosporin is routinely administered to prevent surgical wound infections. In general, antibiotics are continued for 24 to 48 hours post-operatively. It is recommended that liver recipients also receive antimicrobial prophylaxis prior to post-transplant cholangiograms, liver biopsies, and any other manipulations of the biliary tract.

**RENAL TRANSPLANTATION**

**Overview**

The most frequent bacterial complications of renal transplantation arise in the urinary tract. Predisposing factors include renal insufficiency, decreased urine flow through the urinary epithelium, prolonged bladder catheterization, and underlying medical conditions such as diabetes mellitus. The bacteria implicated in such infections are the same as for the general population and include enteric gram-negative bacilli, enterococci, staphylococci, and *P. aeruginosa*.

Surgical wound infections caused by gram-positive cocci and gram-negative bacilli also occur after renal transplantation. Finally, line-related bacteremias can complicate the post-operative course.
Clinical Presentation

Urinary tract infections (UTI) may manifest as acute pyelonephritis and systemic illness with high fever, pain around the graft site, and laboratory data indicative of leukocytosis and active urinary sediment. Alternatively, renal allograft recipients with UTIs can be asymptomatic and present without pyuria. Because of this, a high index of suspicion is required, and routine surveillance urine cultures are often performed after transplantation. In febrile patients, blood cultures are obtained.

Treatment

Choice of therapy for UTIs depends on specific antimicrobial susceptibilities of the bacteria isolated from urine and blood cultures. Fluoroquinolones are widely used in this population; cephalosporins are alternative agents. Anaerobic organisms are rarely involved in these infections and are not routinely covered. For infections caused by coagulase-negative staphylococci or by ampicillin-resistant enterococci, vancomycin is the antimicrobial agent of choice. Length of treatment depends upon the severity of the infection, with two weeks or longer duration of therapy for pyelonephritis. Recurrent infections of the urinary tract prompt further investigation with imaging studies to exclude anatomic abnormalities and obstruction.

Surgical wound infections require appropriate debridement and adjunctive antimicrobial therapy. Empiric coverage is directed at gram-positive cocci and gram-negative bacilli until deep culture data is available to guide antimicrobial therapy.

Prevention

The use of trimethoprim/sulfamethoxazole (TMP/SMX) reduces the incidence of UTIs and blood stream infections after renal transplantation. Such an approach offers additional protection against opportunistic pathogens such as P. carinii, Listeria monocytogenes, and Nocardia species. For sulfa-sensitive recipients, fluoroquinolones are alternative prophylaxis agents. Typically, prophylaxis is continued for six months after transplantation.

To prevent surgical wound infections, a cephalosporin antibiotic is administered peri-operatively and continued for less than 24 hours.

Heart Transplantation

Overview

The main bacterial infection complicating heart transplantation is nosocomially-acquired ventilator-associated pneumonia caused by gram-negative bacteria, including P. aeruginosa, Klebsiella pneumoniae, and the other Enterobacteriaceae. Of special interest are wound infections, especially mid-line sternotomy infections caused by Staphylococcus aureus and coagulase-negative staphylococci. Mediastinitis and line-related bacteremias also occur after heart transplantation. Endocarditis, related to valvular lesions caused by repeated endomyocardial biopsies and colonization by circulating bacteria, is occasionally reported after transplantation.
Clinical Presentation

Pneumonia complicating heart transplantation presents as persistent respiratory failure and inability to wean from mechanical ventilation. In addition, fever may be present, and respiratory secretions are purulent. Radiographic findings that demonstrate consolidative changes aide in the diagnosis and follow-up of patients. Respiratory tract cultures are collected routinely in all mechanically-ventilated patients to determine optimal antimicrobial therapy in the event of an established infection.

Mediastinitis is a serious complication of heart transplantation, presenting as fever, leukocytosis, and signs of systemic toxicity. CT imaging establishes the diagnosis and extent of the infection.

Sternal wound infections may present early in the post-transplantation course as poor healing or dehiscence of the wound or later in the transplant course with sinus tract formation and purulent discharge. CT or nuclear medicine imaging studies may help in defining this infectious process.

Treatment

Antimicrobial therapy for ventilator-associated pneumonia is guided by the results of respiratory tract cultures. Sternal wound infections and mediastinitis require surgical debridement and adjunctive antimicrobial therapy that provides coverage against gram-positive pathogens.

Prevention

Efforts to prevent nosocomial pneumonia include aggressive attempts to wean patients from mechanical ventilation and pulmonary hygiene measures in extubated patients. Peri-operative prophylaxis targeted at gram-positive bacteria may prevent sternal wound infection. Heart transplant recipients are given standard antimicrobial prophylaxis for endocarditis when undergoing any high-risk procedures.

Lung Transplantation

Overview

Pneumonia is a very common complication of lung transplantation, with an overall prevalence of 60% in lung recipients. The heightened susceptibility to lung infection stems from several factors related to the allograft such as impaired cough reflex of the lung allograft, poor mucociliary clearance, ischemia to the explanted lung, abnormal lymphatic drainage, diffuse reperfusion injury, and airway inflammation caused by rejection and resulting in bacterial colonization. After single lung transplantation, the allograft may become infected from the remaining native lung. Gram-negative bacteria, including the Enterobacteriaceae and P. aeruginosa, account for the majority of post-transplant pneumonias. Other important pathogens are S. aureus, H. influenzae, and Streptococcus pneumoniae. B. cepacia colonization is associated with high morbidity and mortality after transplantation for cystic fibrosis.
Mediastinitis and sternal wound infections are other important post-operative infections in lung transplant recipients. The most serious complications after lung transplantation are leakage or dehiscence of the bronchial or tracheal anastomosis.

**Clinical Presentation**

As with heart transplantation, nosocomial pneumonia often presents as persistent respiratory failure requiring ongoing mechanical ventilatory support and the radiographic finding of consolidation. Fever and leukocytosis may be absent. Cultures of lower respiratory tract secretions before and after transplantation are essential for managing these infections. Post-surgical wound infections and mediastinitis present in a manner as described for heart transplant recipients.

**Treatment**

The treatment of pneumonia is guided by the antimicrobial susceptibilities of the pathogens isolated from respiratory tract specimens. Aggressive therapy is warranted, and double antimicrobial regimens are administered to patients infected with *P. aeruginosa*, *B. cepacia*, or multi-drug resistant *Enterobacteriaceae*. Post-surgical wound infections and mediastinitis require debridement and antimicrobial therapy.

**Prevention**

Because of the high risk of infection, lung transplant recipients are given antimicrobial prophylaxis determined by cultures of respiratory tract secretions of both donors and recipients. Very aggressive prophylaxis regimens including two or three antibiotics and inhaled aminoglycosides are considered for patients colonized with *B. cepacia* or other multiply-resistant gram-negative bacteria. Peri-operative prophylaxis is directed at gram-positive bacteria to prevent post-surgical wound infections. After transplantation for cystic fibrosis, antibiotic prophylaxis is continued for 14 days post-transplantation or until purulent respiratory secretions resolve. In addition, some authorities advocate routine sinus surgery in cystic fibrosis patients prior to transplant in order to minimize respiratory infections after transplant.

**Pancreatic Transplantation**

The most common infectious complications after pancreatic transplantation are surgical wound infections and intra-abdominal abscesses. UTIs may occur in recipients who have urinary drainage of exocrine secretions of the allograft because of bacterial overgrowth in the bladder. Other infections have been described after transplant, including abdominal wall cellulitis, peri-pancreatic abscesses, and peritonitis. Important pathogens include gram-positive cocci, followed by gram-negative and anaerobic bacteria.

These infections are managed in a similar manner as described for liver and renal transplant recipients. There are no additional antimicrobial prophylaxis guidelines specific to pancreas transplantation. Trimethaprim-sulfamethoxazole (TMP/SMX) is used to prevent UTI, and standard peri-operative antibiotics are employed.
OTHER IMPORTANT BACTERIAL INFECTIONS

**Nocardia Species**

The incidence of *Nocardia* infections after transplant ranges from 0.7 to 3%, and *N. asteroides* is the most commonly implicated species in most reported series. This infection can present years after organ transplantation. Lung involvement, as evidenced by pneumonia, pulmonary nodules, and abscesses, is common. Less commonly, patients may have brain abscesses, meningitis, and skin involvement. Beaded, branching gram-positive bacilli can be detected on gram-stain of lower respiratory tract specimens and abscess material. The diagnosis is confirmed by the isolation of *Nocardia* species from culture. All patients require imaging of the central nervous system to exclude the possibility of brain abscesses.

The sulfonamides, such as TMP/SMX, are the preferred treatment for nocardiosis. Alternative effective agents include minocycline, the carbapenems, ceftriaxone, cefotaxime, ciprofloxacin, and most recently, linezolid. TMP/SMX, in doses typical for PCP prophylaxis, offers some protection against *Nocardia*.

**Listeria monocytogenes**

Infections caused by *L. monocytogenes* tend to complicate the early post-transplant course, from weeks to the first two months after transplant; however, listeriosis can also present years after transplant. Infection results from the ingestion of contaminated food products. Listeriosis most commonly manifests as central nervous system involvement with meningitis, meningo-encephalitis, or encephalitis, followed by primary bacteremia. More unusual manifestations include pneumonia, arthritis, endophthalmitis, endocarditis, peritonitis, myocarditis, and hepatitis. Patients may present with fever, headache, meningismus, and altered mental status; focal neurological findings and seizures can occur. The cerebral spinal fluid (CSF) analysis reveals polymorphonuclear pleocytosis and hypoglycorrhachia, and the gram stain of the fluid may or may not reveal gram-positive bacilli. The diagnosis is made by the isolation of *L. monocytogenes* from culture of blood and CSF or other sterile site. The treatment of choice is ampicillin in combination with an aminoglycoside, and for patients with penicillin hypersensitivity, TMP/SMX is an alternative agent. TMP/SMX prophylaxis has a protective effect against *Listeria* infections.

**Legionella Species**

Legionellosis, most commonly presenting as pneumonia, can occur at any time after transplantation as a nosocomial or community-acquired infection. It often occurs early in the post-transplant course or coincidentally with steroid therapy or allograft rejection. The presenting symptoms include fever, malaise, chills, dyspnea, chest pain, nonproductive cough, and diarrhea. Radiographic findings include unilateral or bilateral dense pulmonary infiltrates that can progress to cavitation. The diagnosis is made by detecting *Legionella* antigen in urine, direct fluorescent antibody staining of respiratory secretions or tissue specimens, and culturing lower respiratory secretions on supplemented media. Treatment options include the fluoroquinolones, erythromycin, and the newer macrolides. Rifampin
can be added to quinolone or macrolide therapy; however, there are significant drug interactions with the calcineurin inhibitors and prednisone.

**MYCOBACTERIAL INFECTIONS**

**Mycobacterium tuberculosis**

**Overview**

Tuberculosis is considered a serious complication of organ transplantation, with associated mortality approaching 30%. The worldwide incidence of *M. tuberculosis* infections in recipients of organ transplantation is 0.35% to 15%. Transplant recipients are at risk for both primary and reactivation infection, and disseminated infection occurs more frequently than in immunocompetent hosts. The diagnosis and treatment of tuberculosis in this population is often delayed because of atypical and extra-pulmonary presentations of this disease. This infection is rarely transmitted by the allograft.

**Clinical Presentation**

Transplant recipients may present with cavitary pulmonary, genitourinary, intestinal, cutaneous, central nervous system, bone, or disseminated disease. Because these many different presentations, symptoms and signs depend on the site(s) of involvement. Usually, patients have fever accompanied by malaise, night sweats, and weight loss.

The diagnosis of tuberculosis requires a high index of suspicion. The tuberculin skin test is positive in approximately 25% to 33% of infected transplant recipients. Tuberculosis needs to be excluded as a diagnosis in any transplant recipient with pulmonary infiltrates. In cases of suspected tuberculosis, acid fast smears and special cultures are performed on the appropriate clinical specimens. In the event that the initial expectorated sputum and gastric washings are unrevealing, bronchoalveolar lavage or lung biopsy are required to make the diagnosis. Histopathology of biopsy specimens can demonstrate granulomas. All *M. tuberculosis* isolates require susceptibility testing to exclude resistance to anti-tuberculosis agents.

**Treatment**

Transplant patients with active tuberculosis require nine to twelve months of therapy with at least two bactericidal agents to which the isolate is susceptible, preferably with combinations of isoniazid, rifampin, and pyrazinamide. Several regimens are available and have been extensively reviewed in the literature. The treatment of multi-drug resistant tuberculosis poses a particular challenge, and second-line agents must be used. However, outcomes in other immunosuppressed populations have not been very satisfactory, and surgical approaches to eliminate disease are undertaken frequently.

Anti-tuberculous agents have potential toxicities and interactions with immunosuppressive agents: isoniazid is hepatotoxic, rifampin is hepatotoxic, streptomycin is ototoxic and nephrotoxic, and ethambutol may cause optic neuritis.
Rifampin is a potent inducer of hepatic metabolic enzymes. During rifampin therapy, careful monitoring of immunosuppressant drug levels (such as cyclosporine and tacrolimus) is recommended because rifampin therapy is associated with subtherapeutic immunosuppressive drug levels and allograft rejection. Rifabutin may be an alternative agent to rifampin as it has a lesser effect on drug levels.

**Prevention**

Although the majority of transplant candidates are anergic, tuberculin skin testing (PPD) may identify candidates at risk for reactivation tuberculosis and, therefore, is performed during the pre-transplantation evaluation. Chemoprophylaxis with isoniazid for nine to twelve months is recommended in the following situations: recipients with a positive PPD prior to transplantation, radiographic evidence of old active tuberculosis and no prior prophylaxis, a history of inadequately treated tuberculosis, or close contact to a patient with active tuberculosis; recipients of allografts from a known infected or inadequately treated donor; or recipients with a newly positive PPD (recent converters). Chemoprophylaxis may be considered for recipients from highly endemic areas.

**Nontuberculous Mycobacteria**

**Overview**

The mycobacteria other than tuberculosis are occasional causes of post-transplant infections. Such infections typically occur late (years) after transplantation. These organisms are ubiquitous in the environment and include the following pathogens: *M. kansasii*, *M. avium* complex, *M. fortuitum*, *M. chelonae*, *M. marinum*, and *M. abscessus*. *M. marinum* infections are associated with exposure to fresh- or salt-water aquariums or swimming pools.

**Clinical Presentation**

The clinical presentations can vary depending on the site(s) of infection. Frequently, patients present with chronic skin lesions or joint and tendon involvement in the absence of systemic manifestations. Pulmonary and disseminated infections also occur including fever, adenopathy, and intestinal compromise.

The diagnosis relies on biopsy and culture of suspicious lesions. Stains for acid-fast bacilli and special cultures are required on all pathology specimens. Unlike *M. tuberculosis*, granuloma formation is not common.

**Treatment**

Specific treatment recommendations for atypical mycobacterial infections are not available because of their infrequent nature. Treatment is guided by the results of special susceptibility testing of any culture isolates.

Agents effective against *M. avium* complex include clarithromycin or azithromycin, rifabutin, and the fluoroquinolones. *M. fortuitum* infections are typically treated by surgical debridement and adjunctive antimicrobial therapy with one or more of the following agents: cefoxitin, amikacin, imipenem, TMP/
Liver and Intestinal Transplantation

SMX, fluoroquinolones, tetracyclines, and azithromycin or clarithromycin. Agents active against *M. kansasii* include isoniazid, rifampin, and ethambutol. No specific recommendations are available for the prevention of atypical mycobacterial infections in the transplant recipient.

**FUNGAL INFECTIONS**

Fungal infections are a major cause of morbidity and mortality in transplant recipients. The reported incidence ranges from 5% in renal allograft recipients to almost 50% in liver recipients. While most of these infections occur in the first six months after transplantation, fungal infections are occasionally seen several years post-transplantation. The reported mortality for such infections exceeds 30%. Recent advances have been made in the area of antifungal therapy, and the impact of these new therapies on the morbidity and mortality of fungal infections in transplant recipients is currently unknown.

**Candida Species**

**Overview**

The most common source of *Candida* infection is gut translocation or, alternatively, intravascular catheters. The risk factors associated with invasive fungal infection include: the use of high-dose corticosteroids, the administration of broad-spectrum antimicrobials, episodes of allograft rejection requiring increased immunosuppression, and allograft dysfunction. In the case of liver transplantation, the presence of a Roux-en-Y choledocojejunostomy, CMV infection, the administration of OKT3, and re-transplantation are additional risk factors (Table 3).

Recipients of renal allografts are at risk for UTIs with these organisms because of underlying medical conditions, such as diabetes mellitus, and the use of indwelling urinary drainage catheters. Pancreas-kidney recipients also are at additional risk because urinary pH changes associated with exocrine secretion drainage favor bladder colonization with *Candida*.

**Clinical Presentation**

*Candida* infections can present in multiple ways including intravascular catheter infections with sepsis and fever, intra-abdominal abscesses, urinary tract infections. Mediastinitis can complicate heart and lung transplantation.

The diagnosis is made by isolating *Candida* species from culture of appropriate clinical specimens. In the setting of documented or suspected candidemia, fundoscopic eye examination may reveal endophthalmitis or lesions suggestive of septic

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emboli. The role of surveillance cultures for the diagnosis of fungal infections is unknown, as many patients colonized with Candida never demonstrate clinical infection.

**Treatment**
Most Candida species are susceptible to amphotericin B and its lipid-based preparations. Azoles, such as fluconazole and itraconazole, are alternatives for infections caused by C. albicans; however, C. krusei and C. glabrata demonstrate significant resistance to these agents. Lipid-based amphotericin B preparations are less nephrotoxic as compared to conventional amphotericin B. This benefit is offset by greater expense and less clinical experience with their use. New antifungal agents such as caspofungin, an echinocandin, and voriconazole, a triazole, have activity against Candida species, but extensive clinical experience is lacking. Potential drug interactions exist for both the azoles and the echinocandins with the immunosuppressant agents.

**Prevention**
For liver transplant recipients, oral bowel decontamination with nystatin decreases the rate of gut colonization with Candida species, but its benefit in reducing post-operative fungal infections is unclear. Although fluconazole has demonstrated efficacy in the prevention of Candida infection after liver transplantation, its universal use is discouraged because of the potential for emergence of azole-resistant fungi. Fluconazole prophylaxis is acceptable for high risk liver allograft recipients, especially in the setting of repeated surgeries, prolonged operation time, renal failure, and high intra-operative transfusion requirement. Fluconazole courses beyond four weeks are not warranted. In kidney and pancreas-kidney recipients, pre-emptive treatment of asymptomatic candiduria may be indicated. There is anecdotal efficacy reported with fluconazole prophylaxis after pancreas transplantation, and it may be considered for high risk recipients such as those with an enteric drainage procedure, pancreas after kidney transplantation, peritoneal dialysis before transplantation, reperfusion pancreatitis, and re-transplantation.

**Aspergillus Species**

**Overview**
Invasive aspergillosis is one of the most devastating infectious complications of organ transplantation. The incidence of this infection ranges between 1-2% in liver and kidney allograft recipients, 5% heart recipients, and up to 15% of lung recipients. The portal of entry in the vast majority of cases is the respiratory tract through environmental exposures. Once in lung tissue, Aspergillus causes ulceration, necrosis, and tissue and blood vessel invasion. Once angioinvasive, dissemination to distant sites occurs. While, historically, most infections present in the first three months following transplantation, recent trends suggest that late onset infections are occurring more frequently than in the past. Risk factors for invasive disease include prolonged operation time, renal failure, neutropenia, CMV infec-
tion, and heavy immunosuppression, especially high dose corticosteroids and OKT3. Additional risk factors for liver recipients include allograft dysfunction, fulminant hepatic failure before transplantation, and re-transplantation. For lung recipients, airway specimen cultures positive for *Aspergillus* and obliterative bronchiolitis are risk factors.

**Clinical Presentation**
The clinical presentation depends on the site(s) of infection. Respiratory symptoms such as dyspnea, cough, pleuritic chest pain, and fever predominate. Hemoptysis is a sign of invasive disease. *Aspergillus* disseminates to the brain, liver, spleen, kidneys, heart, blood vessels, bone, joints, and gastrointestinal tract.

The diagnosis of invasive infection with *Aspergillus* relies on the isolation of the organism in the appropriate setting; histopathology of biopsy specimens is required to determine invasiveness when this mold is recovered from respiratory specimens. CT imaging is helpful in evaluating lung disease, and CNS imaging by CT and MR will delineate brain abscesses. The isolation of *Aspergillus* species from the respiratory secretions of any transplant recipient requires a prompt and thorough investigation to exclude invasive infection; this is especially true for lung allograft recipients.

**Treatment**
Recent studies have demonstrated that voriconazole has greater efficacy than amphotericin B for the treatment of invasive aspergillosis. This offers some promise given that invasive aspergillosis carries an 80% to 100% mortality rate, even with the use of amphotericin B. Caspofungin is also approved for the treatment of refractory aspergillosis. Extensive clinical experience with these new agents is lacking, and the role of combination therapy for invasive mold infections has not been studied.

**Prevention**
There are no firm recommendations for prophylaxis against *Aspergillus* infections in transplant recipients. Some advocate the use liposomal amphotericin B in select high risk liver recipients; however, this approach is not without expense or potential significant toxicity. In lung and heart-lung recipients, inhaled amphotericin B may reduce the frequency of *Aspergillus* infections. Some centers advocate the use of oral itraconazole for lung recipients with demonstrated airway colonization by *Aspergillus* species.

**Zygomycosis**
Infections caused by molds, such as *Rhizopus* species, *Mucor* species, and *Absidia* species, are reported in up to 9% of transplant recipients. Exposure occurs as a result of inhalation or cutaneous inoculation of spores. Risk factors for such infections include corticosteroid therapy, metabolic abnormalities such as diabetic ketoacidosis, or deferoxamine therapy. Typical clinical presentations include
rhinocerebral infection, nodular or cavitary pulmonary disease, gastrointestinal involvement, skin and soft tissue infection, and disseminated disease. The diagnosis is made by biopsy of involved areas, both by histopathology and culture. Amphotericin B remains the therapy of choice, although surgical debridement is the optimal therapy to control these, often fatal, infections.

**Cryptococcus neoformans**

**Overview**

*Cryptococcus neoformans*, a fungus present in soil and bird-droppings, is acquired by inhalation. Infections caused by *C. neoformans* occur throughout the post-transplant course, and only approximately one half of cases occur within the first year after transplantation.

**Clinical Presentation**

This fungus has a strong predilection for the central nervous system, causing meningitis and, occasionally, brain abscesses. Patients present subacutely with low-grade temperature, headache, and altered mental status. Signs of frank meningismus are usually absent. Alternate presentations include pulmonary disease with pneumonitis, nodules, and lung abscess; soft tissue, skin or joint infection; and fever of unknown origin.

The diagnosis of cryptococcosis is made by the detection of antigen in serum and CSF. Examination of the CSF is required in any transplant recipient who presents with cryptococcal infection from any site. With meningitis, the CSF analysis demonstrates lymphocytic pleocytosis, elevated protein, and low glucose; the opening pressure is elevated. Fungal cultures of CSF and blood should be performed.

**Treatment**

Amphotericin B is the treatment of choice for cryptococcal infection. 5-flucytosine may be added to amphotericin B for the first phase of treatment. Fluconazole has been used to treat meningitis in other patient populations but is not well studied in transplant recipients.

The total duration of treatment for cryptococcosis is a minimum of eight to ten weeks. Meningitis is initially treated with amphotericin B for the first two weeks followed by fluconazole for the remainder of therapy. Important adjunctive measures include repeated lumbar punctures to relieve elevated intracranial pressure, repeat analysis of CSF to monitor response to therapy, and periodic monitoring of the serum cryptococcal antigen to detect relapses.

**Prevention**

Primary prophylaxis directed against *C. neoformans* is not advocated. It remains unclear whether secondary prophylaxis or suppression with fluconazole is necessary in transplant recipients who have completed treatment for cryptococcal infection.
PNEUMOCYSTIS CARINII

Overview
Infections caused by *P. carinii* occur during the first six months after transplantation in organ recipients who are not receiving prophylaxis. With appropriate prophylaxis, this infection has been effectively eliminated in transplant recipients.

Clinical Presentation
Patients present subacutely with fever, dyspnea, and nonproductive cough. The classic radiographic finding is bilateral diffuse interstitial and alveolar infiltrates. The laboratory evaluation reveals elevated lactate dehydrogenase (LDH) levels and hypoxemia. The definitive diagnosis is made by direct staining of induced sputum, bronchoalveolar lavage, or lung tissue specimens with fluorescent monoclonal antibodies, methenamine silver, calcofluor white, or Wright-Giemsa stain. Co-infection with CMV can occur and requires investigation.

Treatment
Pneumonitis caused by *P. carinii* is treated with high-dose TMP/SMX, 15 to 20 mg/kg/day, for a duration of 21 days. In cases associated with severe hypoxemia, adjunctive corticosteroid therapy is warranted. For patients intolerant of TMP/SMX, pentamidine, clindamycin plus primaquine, and atovaquone are alternative treatment options.

Prevention
Low-dose TMP/SMX, one single or double strength tablet daily, administered for six months after transplantation has effectively reduced the incidence of post-transplant PCP. Alternative regimens are dapsone, aerosolized pentamidine, and atovaquone. Patients with ongoing significant immunosuppression, allograft rejection, and allograft dysfunction require a longer period of prophylaxis.

ENDEMIC MYCOSES
The endemic mycotic pathogens include *H. capsulatum*, *C. immitis*, *Blastomyces dermatitidis*, and *Paracoccidioides brasiliensis*. These infections occur at any point after transplantation as a result of primary acquisition or reactivation of disease. It is unclear whether blastomycosis or paracoccidiomycosis occur at any greater frequency in transplant recipients than in the general population.

Organ recipients who reside or who have traveled to the southwestern United States or northern Mexico, and certain areas of Latin America are at risk for coccidioidomycosis. Common clinical presentations include disseminated and pulmonary infection. Patients present with nonspecific symptoms such as fever, night sweats, malaise, cough, and dyspnea. Chest radiographic findings include interstitial, alveolar, nodular, or lobar infiltrates; a miliary pattern; cavitary lesions; and hilar adenopathy. Other potential sites of infection include the blood, skin, brain, liver, urine, bone and joints, and muscle, including myocardium. The diagnosis is made by serology, histopathology, and culture. The treatment of choice is amphotericin B, and an alternative agent is fluconazole.
Histoplasmosis is endemic in the central United States, along the Ohio and Mississippi River Valleys, as well as many other countries. This infection usually occurs as a result of inhalation, and transmission by the allograft has been documented. Disseminated infection is the most common presentation in transplant recipients, whose symptoms are nonspecific, including fever, night sweats, non-productive cough, headache, myalgias, and mucocutaneous lesions. Hepatosplenomegaly and pancytopenia may be present. Chest radiographic findings include interstitial or miliary infiltrates, focal consolidation, and hilar adenopathy. The diagnosis is made by serologic testing, direct detection of antigen in urine, histopathology, and culture of appropriate specimens such as respiratory tract secretions and tissue, blood, bone marrow, and other affected tissues. The treatment of choice is amphotericin B; alternative agents include the lipid-based amphotericins and itraconazole.

There are no firm recommendations for prevention of the endemic mycotic infections after transplant; some centers advocate pre-transplantation screening of at-risk candidates by serologic testing and chest radiography and azole prophylaxis for candidates with evidence of prior infection.

VIRAL INFECTIONS

Viruses are important pathogens associated with significant post-transplant morbidity and mortality. Viral infections result from acquisition of new infection or reactivation of latent viruses. The herpesviruses, in particular, are responsible for common and, sometimes, severe infection syndromes in the transplanted host.

CYTOMEGALOVIRUS

Overview

Cytomegalovirus is the most common infection in transplant recipients after the first month post-transplantation. For the transplant recipient, CMV has three major implications: it causes disease associated with substantial morbidity and mortality, it augments immunosuppression that is associated with increased risk of PCP and other infections, and it is associated with allograft rejection. After transplantation, CMV disease is defined as symptomatic viremia or end-organ infection. Most individuals develop CMV infection at some point during their lifetime, and after the acute phase of the illness, the virus persists in a latent stage within the host. Depending on the recipient’s and donor’s previous exposure to the virus, transplant recipients are at different risk of developing CMV disease post-transplantation. Thus, three patterns of infection are observed:

1. Primary infection occurs when a CMV-seronegative allograft recipient receives cells latently infected with CMV from a seropositive donor, resulting in viral reactivation (CMV donor+, recipient-).
2. Reactivation infection occurs when endogenous latent virus reactivates in a seropositive recipient (CMV D+ or -, R+).
3. Superinfection (reinfection) occurs when a seropositive recipient receives an organ from a seropositive donor and the virus that reactivates is that of donor origin (CMV D+, R+).
The D+R- patients represent the highest risk group for the development of post-transplant CMV disease, with up to 60% of recipients in this category manifesting this infection. Lower risk groups are the D+R+ and D-R+ in which the incidence of CMV disease ranges from 20-40%. The use of anti-lymphocyte therapies such as OKT3 for induction or rejection increases the risk of any seropositive recipient (R+) for CMV disease, such that these recipients are treated as another high risk group. The D-R- group represents the lowest risk group and may rarely develop primary infection after receipt of unscreened blood products or community exposure. Based on historical data, depending on the organ transplanted, lung and gut recipients are at high risk for CMV disease, whereas liver, pancreas, and heart recipients fall into an intermediate category, and renal transplant recipients represent the lowest risk group.

**Clinical Presentation**

Cytomegalovirus disease is found most commonly one to four months after transplantation. Manifestations of CMV range from asymptomatic viremia to lethal disseminated disease. Mild to moderate disease presents with fever, malaise, headache, arthralgias and myalgias. Laboratory abnormalities include leukopenia and thrombocytopenia. End organ involvement usually correlates with the type of transplant, thus, hepatitis occurs in liver recipients, glomerulopathy in renal transplants, pancreatitis in pancreatic transplants, and pneumonitis in lung and heart-lung recipients. Other organs that can be affected are the gut (gastritis, esophagitis, colitis), central nervous system (encephalitis, polyradiculopathy), and retina (retinitis). Colitis usually presents with diarrhea that is occasionally bloody, and it may be complicated by the formation of ulcers and perforation. Retinitis is significantly less common in transplant recipients than in patients with HIV infection.

Laboratory abnormalities with CMV end-organ involvement depend on the affected organ system. CMV pneumonitis appears radiographically as bilateral interstitial, unilobar, and nodular infiltrates. Hepatitis manifests with elevated transaminases, alkaline phosphatase, and gamma-glutamyltransferase with minimal increases in bilirubin levels. The definitive diagnosis of CMV organ involvement often requires biopsy of the affected organ and pathologic demonstration of inclusion bodies or detection of CMV in tissue by immunohistochemistry or in-situ hybridization techniques.

To detect replicating virus in fluids or tissue, several techniques have been used including tube cell culture that demonstrates the cytopathic effect of the virus after 7-14 days of incubation and rapid shell-vial culture that uses fluorescent labeled antibodies and yields results in a shorter period of time, usually after 24-48 hours. Serologic testing is not reliable for the diagnosis of acute CMV infection.

Rapid tests that detect early disease are blood CMV antigenemia and PCR techniques. These two methods are used to determine which patients may benefit from preemptive administration of antiviral drugs in an effort to avoid the development of overt CMV disease.
Treatment

The currently available antivirals for the treatment and prevention of CMV disease are acyclovir, valacyclovir, ganciclovir, valganciclovir, foscarnet, and cidofovir. Acyclovir, valacyclovir, ganciclovir, and valganciclovir are available in oral formulations. CMV hyperimmune globulin is available in different preparations as well.

Treatment of established CMV disease currently relies on the intravenous administration of ganciclovir. Induction treatment at doses of 5 mg/kg twice daily are used, and maintenance doses are 5 mg/kg/daily. Duration of treatment varies depending on the severity of the disease; viremia may be treated with a regimen of 14 days at full doses whereas end-organ involvement usually requires longer courses. Oral ganciclovir has been used as maintenance therapy to prevent relapses of CMV. Valganciclovir offers improved oral bioavailability over GCV; however, limited clinical data are available to support its routine use for the treatment of transplant-related CMV infection. Side effects of GCV include bone marrow suppression, hemolysis, renal toxicity, rash, liver function abnormalities, and infusion site reactions.

D+R- patients with CMV infection who have received multiple courses of ganciclovir are at risk for the development of antiviral drug resistance. Ganciclovir resistance, usually caused by viral mutations in the UL97 gene, must be considered in patients with poor clinical response or persistent viral shedding during treatment.

The use of foscarnet in transplant recipients is less well studied. Side effects of this drug include nephrotoxicity, hyper- and hypophosphatemia, hyper- and hypocalcemia, nausea, vomiting, and seizures. Its use is reserved for patients who are intolerant of or have failed to respond to GCV.

Some centers advocate CMV hyperimmune globulin as an adjunctive therapy for CMV disease but other studies fail to confirm its effectiveness. Combination of this agent with GCV may be useful, especially in patients with severe life-threatening disease, such as CMV pneumonitis.

Prevention

There are two main strategies for the prevention of CMV disease after transplantation. The first is the administration of antiviral prophylaxis to prevent the occurrence of CMV disease. The second approach is pre-emptive therapy, whereby patients at risk are monitored for laboratory evidence of subclinical CMV infection, usually by the CMV antigenemia or quantitative CMV PCR assay, and initiated on antiviral therapy if subclinical infection is detected. There is significant debate in the literature in regards to the effectiveness of these different approaches for the prevention of CMV disease, although both strategies are acceptable practices.

In general, the pre-emptive therapy strategy is effective in CMV-seropositive recipient groups. However, D+R- patients require oral GCV prophylactically. Because of improved oral availability, many centers now use valganciclovir instead of GCV, although clinical data is lacking. Data on renal transplant recipients
suggests that valacyclovir is an effective alternative in this population. Patients in any group, except D-R-, receiving OKT3 or anti-lymphocyte antibodies are considered candidates for GCV prophylaxis since their risk of CMV disease is substantially increased. Prophylaxis is continued for the first three months after transplantation. One exception to this approach is lung and heart-lung recipients that fall into the D+R- group; since they are at the highest risk, intravenous full dose GCV for two weeks and followed by maintenance doses to complete three months of prophylaxis after transplantation seem warranted to prevent severe disease.

For individuals in the D-R- group, CMV-negative blood products are administered if needed to prevent primary CMV infection and subsequent risk of disease.

**EPSTEIN-BARR VIRUS**

**Overview**

Epstein-Barr virus infection plays an important role in the development of post-transplant lymphoproliferative disorder (PTLD). Most transplant recipients have been infected with EBV at some point during their lifetime, and the virus persists within the host in a latent state. The pathogenesis of PTLD involves the heightened replication of EBV-infected lymphocytes triggered by agents such as OKT3 and the polyclonal anti-lymphocyte globulins. In addition, immunosuppression impairs the ability of virus-specific cytotoxic T-lymphocytes to control the expression of EBV-infected transformed B-cells, leading to the polyclonal and monoclonal proliferation of lymphocytes that constitutes PTLD. EBV may be of donor origin in EBV-seronegative recipients who receive an organ from a seropositive individual.

The incidence of PTLD ranges from 1% to more than 20% depending on the organ transplanted: 1% in renal transplant recipients, 2% in liver recipients, 2-4% in heart recipients, 2-8% in lung recipients, 11% in kidney-pancreas recipients, 7-11% in intestine recipients, and 13-33% in multi-organ recipients. Risk factors associated with the development of PTLD include EBV-seronegativity prior to transplantation, OKT3 or polyclonal anti-lymphocyte antibody therapy, CMV seromismatch, and CMV disease. Primary EBV infection is a strong predictor of PTLD.

**Clinical Presentation**

Primary infection with EBV may cause a syndrome characterized by malaise, fever, headaches, and sore throat. PTLD may develop at any time post-transplantation manifesting as a mononucleosis syndrome with fever, adenopathy, and sore throat; fever of unknown origin; allograft dysfunction; respiratory symptoms with pulmonary infiltrates; and weight loss. The definitive diagnosis of PTLD relies on histopathologic examination of biopsy specimens. Quantitative PCR techniques may help determine patients at high risk for the development of this disease before overt signs and symptoms manifest; however, this approach remains experimental.
Treatment

Once PTLD is established, the effectiveness of antiviral treatment has been disappointing. The main therapeutic approach in these cases is reduction of immunosuppression to the extent possible. Multifocal disease with organ involvement carries the worst prognosis, and in this setting, chemotherapy or radiotherapy is usually indicated. An alternative option is immunotherapy based on sensitized T-lymphocytes obtained from patients before transplant and stimulated ex vivo; such therapy is under investigation and is showing promising results.

Prevention

In EBV-seronegative patients, the use of EBV-seronegative organs constitutes the best option to prevent PTLD, especially in high-risk groups such as lung, gut, and pancreas recipients. It is unclear whether GCV is effective for the prevention of EBV-associated PTLD. Some data suggest that intravenous GCV followed by oral acyclovir during the first three months following transplantation decreases the incidence of PTLD in liver, kidney, and kidney-pancreas EBV-seronegative recipients, but there is not enough data to recommend this approach.

Herpes Simplex Virus

Overview

Infection with HSV in transplant recipients most commonly represents reactivation of latent virus. Up to 80% of adult transplant recipients are seropositive for HSV, indicating prior infection. Following primary infection, HSV remains latent in sensory nerve ganglia, and reactivation often occurs during the first month post-transplantation in up to 40% of organ recipients. The use of OKT3 is associated with higher frequency of reactivation.

Clinical Presentation

HSV reactivation most often manifests as oral or genital mucocutaneous lesions. Because of depressed cell-mediated immunity, organ recipients are at risk for more severe disease, delayed healing of skin lesions, and occasionally, visceral or disseminated involvement such as pneumonitis, tracheobronchitis, esophagitis, or hepatitis.

Mucocutaneous involvement presents as painful vesicular and ulcerative lesions; the appearance may be different than that observed in immunocompetent individuals. Pneumonitis is rare and usually seen in conjunction with other pulmonary infections. Ulcerative esophagitis manifests as dysphagia and odynophagia and can resemble or occur concomitantly with candidiasis. Hepatitis may occur and be rapidly progressive and fatal. Disseminated HSV is occasionally reported. Encephalitis is not seen with greater frequency than in immunocompetent individuals.

The diagnosis of HSV is made by direct immunofluorescent antibody staining, Tzanck smear, or culture of tissue and body fluids. Serodiagnosis is possible if IgM is detected or a four-fold rise in IgG titers is noted. In the case of HSV pneumonitis, the definitive diagnosis relies on histopathologic examination of biopsy specimens,
since the recovery of HSV from tracheal secretions may represent reactivation of virus in the oropharyngeal cavity.

**Treatment**

Acyclovir is considered the treatment of choice for HSV infections. Oral administration of 200 mg five times daily is effective in mild disease. Alternative oral preparations with better bioavailability are valacyclovir and famciclovir. Serious cases with disseminated infection or organ involvement require treatment with intravenous acyclovir. Acyclovir may cause nephrotoxicity due to the precipitation of drug crystals in the renal tubules; other serious side effects include confusion, delirium, and seizures. The dose of acyclovir is adjusted according to the creatinine clearance. Acyclovir resistance has occurred in organ transplant recipients with HSV infection; foscarnet is considered the drug of choice in this situation.

**Prevention**

The use of low-dose acyclovir (200 mg every six to eight hours) for the first month after transplantation is an effective prophylactic regimen in all seropositive transplant recipients. Other potential options are valacyclovir and famciclovir.

**VARICELLA ZOSTER VIRUS**

**Overview**

Post-transplantation, VZV causes herpes zoster in seropositive individuals (90% of the adult population). The remaining 10% of patients are at a risk for primary infection. Up to 13% of transplant recipients develop herpes zoster during the first six months post-transplantation.

**Clinical Presentation**

Typical dermatomal skin lesions are the usual presentation of herpes zoster. Disseminated disease occurs as well, with multiple dermatome involvement. Dermatomal pain without skin eruption has been described.

Primary VZV infection is transmitted via contact with infected individuals; it may occur at any time after transplant and is potentially serious with pneumonia, skin lesions, hepatitis, encephalitis, pancreatitis, and disseminated intravascular coagulation.

The diagnosis is most often made clinically, but culture of VZV and direct immunofluorescent antibody staining or Tzanck smear of appropriate clinical specimens are used for confirmatory purposes.

**Treatment**

The treatment of localized dermatomal zoster is treated with oral acyclovir, valacyclovir, or famciclovir. In severe cases, disseminated disease, or primary infection, intravenous acyclovir is administered initially and patients are monitored carefully. The duration of treatment is usually ten days.
Infections in Transplant Recipients

**Prevention**

Varicella immune-globulin is administered to VZV-seronegative recipients exposed to acutely infected individuals. Prophylactic low-dose oral acyclovir may prevent VZV infections although this has not been formally studied.

**Other Viruses**

Human herpesviruses 6 and 7 reactivate after transplantation. The role of these viruses in clinical disease is currently under active investigation, as well as their interactions with other pathogens such as CMV and role in allograft rejection. There are no standard assays available for the diagnosis of these infections.

Hepatitis B and C viruses are common causes of end-stage liver disease and important indications for liver transplantation. The risk of recurrent infection with either virus is more than 80% after transplantation and morbidity can be high, especially in the case of hepatitis B. Viral hepatitis may be transmitted to recipients by the organs of infected donors. There is considerable ongoing debate regarding the use of organs from infected donors (mainly hepatitis C) in emergent transplantation of live-saving organs, and consensus has not been reached.

The polyomaviruses, BK virus (BKV) and JC virus (JCV), are ubiquitous viruses that cause subclinical and latent infections in humans. 80% of the adult population is seropositive for each of these viruses. These viruses may reactivate in the setting of immunosuppression, resulting in distinctive clinical syndromes. BKV reactivation after renal transplantation may result in tubulointerstitial nephritis, leading to progressive allograft dysfunction and eventual graft loss. In addition, BKV reactivation may present as ureteral stenosis leading to obstructive nephropathy. The diagnosis of BK nephropathy is suggested by the presence of characteristic “decoy” cells on cytologic examination of urine. Because the histopathological findings may be confused with allograft rejection, the definitive diagnosis is established by the demonstration of polyomavirus inclusions in renal biopsy specimens. The use of PCR assays with blood and urine specimens for the diagnosis of BK nephropathy are being investigated. Progressive multifocal leukoencephalopathy, caused by the JCV, is less commonly encountered in organ recipients than in patients with acquired immunodeficiency syndrome. Treatment for polyomavirus infections has generally focused on supportive care and reduction of immunosuppression. A variety of antiviral agents are under investigation, with cidofovir demonstrating some promise.

Transplant recipients are also at heightened risk of developing infection with the related human papillomaviruses. These viruses are associated with neoplasms such as squamous carcinoma of the cervix. An association with skin carcinomas has been suggested but not definitively confirmed.

Parvovirus B19 infection may cause profound aplastic anemia after transplantation. Other respiratory viruses with potential to cause severe disease in transplant recipients include the respiratory syncytial virus, the adenoviruses, and the influenza viruses.
PARASITIC INFECTIONS

Strongyloides stercoralis and Toxoplasma gondii warrant special attention because of the distinctive features of these pathogens and the potential for severe infection in organ transplant recipients.

STRONGYLOIDES STERCORALIS

Overview

Strongyloidiasis is a helminthic infection endemic to tropical and subtropical areas of the world, including Southeast Asia, the Caribbean, and West Africa. Rural areas of Kentucky, Tennessee, and Louisiana are the endemic foci within the United States. Infection results in a diarrheal illness with peripheral eosinophilia, but the organism can be maintained in the gastrointestinal tract asymptotically for decades. The lifecycle of S. stercoralis is complex and unique in that autoinfection of the host occurs; larvae transform into an infectious form in the intestine and invade the intestinal mucosa and perianal skin. This process maintains the infection by constant re-introduction of infectious forms into the hosts. In immunocompromised patients, autoinfection may result in the hyperinfection syndrome, a form of disseminated strongyloidiasis in which an accelerated lifecycle and excessive helminth burden occur. The mortality rate of hyperinfection syndrome approaches 70%. A complication of this syndrome is gram-negative bacteremias and shock caused by the disruption of normal intestinal barriers during invasion of the gut mucosa by larvae.

Clinical Presentation

In patients harboring S. stercoralis, symptoms develop in the first six months after transplantation. The intestinal form presents as abdominal pain, diarrhea, nausea, and vomiting. Hyperinfection syndrome presents with tachypnea, respiratory distress, cough, hemoptysis, and enterocolitis. Fever and rash may also be present. The chest radiograph demonstrates alveolar or interstitial infiltrates. On laboratory data, eosinophilia, if present, is helpful.

The definitive diagnosis is made by examining stool specimens for the presence of larvae. The sensitivity of this method is improved by the examination of multiple specimens and concentration techniques. Sputum and duodenal aspirates may be examined for the presence of larvae. Serologic testing is also available.

Treatment

The treatment options for strongyloidiasis include ivermectin, 200 mcg/kg/day for two days; albendazole, 400 mg/day for three days; or thiabendazole, 25 mg/kg for two days. The hyperinfection syndrome requires seven to ten days of therapy. Secondary bacteremias are treated with antimicrobial agents.

Prevention

Prevention is aimed at candidates who have resided or traveled extensively to endemic areas. Prior to transplantation, candidates are screened for the presence
of this infection, either serologically or by examination of multiple stool specimens for larvae. Established infection is treated before transplant. Interestingly, cyclosporine A (CsA) has activity against \textit{S. stercoralis}; recipients treated with CsA are less likely to develop the hyperinfection syndrome.

\textbf{Toxoplasma gondii}

\textbf{Overview}

Toxoplasmosis after transplantation is most frequently caused by reactivation of latent disease. Seronegative heart transplant recipients are at the greatest risk for developing this disease when receiving an organ from a seropositive donor; in such cases, the risk of primary infection is 50% if prophylaxis is not administered. This infection is also potentially transmitted by other organs, such as liver, and blood products.

\textbf{Clinical Presentation}

Most infections occur during the first two months after transplantation. Primary infection manifests as fever, malaise, and generalized lymphadenopathy. Other presentations include meningo-encephalitis, pneumonitis, pericarditis, myocarditis, and retinitis.

The definitive diagnosis is made by the histologic demonstration of trophozoites surrounded by inflammatory reaction. Serologic testing is not very helpful for the diagnosis of infection.

\textbf{Treatment}

The options for therapy are one of the following: pyrimethamine and sulfadiazine or pyrimethamine plus clindamycin. Folinic acid is administered with either regimen to prevent myelotoxicity. Treatment is continued for two to three weeks after resolution of the acute infection.

\textbf{Prevention}

After transplantation, toxoplasmosis is prevented by the use of TMP/SMX in the same doses used for PCP prophylaxis for at least six months. Pyrimethamine is an alternative agent for sulfa-intolerant patients. All heart transplant candidates and donors require serologic screening to determine the post-transplant risk of toxoplasmosis.

\textbf{Vaccination in Transplant Recipients}

Two issues limit the overall effectiveness of vaccination strategies in transplant recipients. First, transplant recipients may have declining antibody levels and diminished antibody responses to previous vaccine antigens once they become severely immunosuppressed (loss of previous immunity). Secondly, available evidence suggests that transplant recipients have diminished, although not absent, responsiveness to immunization (reduced vaccine efficacy). This is best demonstrated in kidney, liver and heart recipients after immunization with the pneumococcal vaccine.
Solid organ transplant recipients require periodic assessment of immunization status for vaccine-preventable illnesses, beginning during the pre-transplantation evaluation. Routine immunizations are administered or updated as long as possible before the transplant to allow for the development of immunity; these vaccinations include the hepatitis B series, hepatitis A, pneumococcal, yearly influenza, and tetanus-diphtheria. For VZV-seronegative transplant candidates, immunization with the varicella vaccine should be considered. In general, live attenuated virus vaccines are contraindicated in severely immunosuppressed hosts because of the potential for viral reactivation. Also, household contacts of transplant recipients should not undergo immunization with live viruses because of the potential for secondary infections.

**SELECTED READINGS**

Psychiatric Issues in Organ Transplantation

John E. Franklin and Roslyn M. Paine

The myriad of technical advances in solid organ transplant over the past 20 years has challenged the field in expected and unexpected ways. The increased survival rates and quality of life has increased referrals and demand for organ transplantation. This increased demand however has highlighted the shortage of available donor organs. This dilemma serves as a backdrop to many of the psychosocial issues discussed in this Chapter. These issues include selection criteria, dealing with long waits for transplant, the anxiety of where to list and rule changes in allocation of organs. Hopefully with advances in areas such as xeno-transplantation, artificial organs, islet cell transplants, split livers and increased donor registration some of the issues discussed here will become relatively mute, much as risk/benefit data has made transplantation decisions relatively easy for patients and physicians in recent years. This chapter will be divided into (1) what transplant personnel should know about the general psychosocial care of transplantation patients; (2) the role of mental health specialists in transplant; (3) specific issues regarding liver, small bowel, kidney, pancreas, heart and lung transplants.

GENERAL PSYCHOSOCIAL ISSUES IN TRANSPLANTATION

PATIENT, FAMILY EVALUATIONS

Why do some patients come to transplant and many others who meet medical criteria do not? The selection process includes such factors as primary physician awareness, patient knowledge base and motivation, health status, family and friends, managed care companies and geographical location. When we encounter patients on the transplant service, they, on some level, have cleared some of these hurdles. Much of the selection process has happened before patients come for their first transplant clinic evaluation. This is important to realize, as much of our job is to create a supportive and therapeutic environment to get patients through not only the medical challenges, but also psychosocial challenges of transplant. What often makes the challenge of supporting patients more difficult is the geographic distances to transplant centers, managed care concerns that have the potential of fracturing care and the need for communication between multiple medical services. It must be kept in mind the maze of tests, medical people and often frustrating systems that patients undergoing transplant are interfacing. Although this is burdensome to patients, this process has the potential for building good therapeutic alliances between patient/institutions and it provides an observation.
period of the patient’s strengths and weaknesses and their coping mechanisms. A patient may fail this test, such as a patient who relapses to alcohol or drugs or patients who become grossly noncompliant with medical care. Although these situations may make transplant doubtful, we need to determine what is going on and respond in a therapeutic way. For the relapsing alcoholic, it may be referral for rehabilitation with the possibility of being active on transplant list post rehabilitation. For patients who are noncompliant, a referral to another transplant center might be appropriate. However, for the vast majority of “transgressions” by patients we want to understand issues from the patient’s perspective, maintain clear expectations and help identify and support patient positive coping mechanisms.

Table 1 outlines the general psychosocial evaluation format for all solid organ transplants. Several visits may be necessary before a thorough evaluation can be completed. The patient’s energy level, mental status and the presence or lack of presence of family may play an important factor. In general, it is always preferable to have patients bring family members with them for psychosocial evaluations. Family members often provide information that the patient cannot and can collaborate important information such as recent substance use. Their presence at the meeting also provides an important opportunity to observe family dynamics. It is equally important in certain instances to interview patients and families separately to allow them to express any concerns or questions they may have. Family members may be reluctant to say anything that jeopardizes transplant candidacy. Potential donors may have ambivalence about donation or organ recipients may express a feeling of pressure to undergo a procedure they do not want. Even the timeliness of scheduling appointments can be instructive as to motivation or ability to follow through. Some patients and families are fairly sophisticated regarding medical issues. This apparent sophistication may belie underlying psychosocial difficulties in the family. On the other hand, some patients and families present so chaotically initially that it seems they will not make it through the procedure, but they do. Medical personal should be careful not to make unalterable judgments of people based on initial presentation, personnel

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<td>— Review of medical history and patient’s perspective of illness</td>
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<td>— Meet with family together or separately</td>
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<td>— Assess patient motivation and sophistication</td>
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<td>— Listen for patient concerns</td>
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<td>— Urine toxicology as necessary</td>
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bias or third party information. It is the practice of many transplant centers to have a multidisciplinary conference where patient candidacies are discussed. The benefit of this approach includes the advantage of assessing people who have interacted with the team in different settings. Surgeons, other physicians, nurses, social workers, etc., in addition to the mental health specialists, all have observational skills important to understanding a patient situation. An opportunity for all staff to air support and concerns about a patient’s candidacy results in consensus decisions that are usually, but not always correct. In addition, it creates a more cohesive staff and provides clearer messages to patients and families. It is important to realize that it is not only physicians caring for and taking responsibility for these patients. Health care providers such as nurse coordinators, social workers, ICU nurses and floor nurses feel acutely the stress of caring so intensely for transplant patients. Making everyone feel some part of the decision making and policy of selection is important. A number of prognostic rating scales for psychosocial functioning in transplantation have been devised. The Psychosocial Assessment of Candidates for Transplant (PACT) is a general rating scale that can be used for all solid organs. However, these rating scales need further validation and the fact is there will always be exceptions to the rule. Sometimes the experienced evaluator will have hunches or are able to draw on similar experiences with similar patients to help with patient selection.

The issue of patient selection is important to all transplants; however, as we will discuss later, areas such as liver transplantation in recovering alcoholics, still create controversy and misunderstanding. Sometimes there are situations where the patient clearly contributed to the rejection by noncompliance with medications. The experience for most patients who experience organ rejection is often one of shock, disappointment, sadness and unexpressed guilt. The decision to retransplant has to be carefully weighted. The reasons for non-compliance have to be fully understood and the transplant team has to be convinced that it will not happen again. Unfortunately, at this time many patients die awaiting transplant, which is particularly difficult for families and medical staff to accept. Patient and family support groups can be very helpful to help with the process, give practical advice and emotional support. Many patients and families contribute time in organizations such as The Transplant Recipient International Organization (TRIO), which provides patient information and promotes donor registration.

**Absolute vs. Relative Contraindications for Transplant**

A survey was conducted by UNOS regarding the transplantation selection processes of the vast majority of U.S. transplantation centers. At most centers active substance abuse and major psychiatric disorders such as schizophrenia were judged to be close to absolute contraindications for transplant. In the real world, however, exceptions are granted based on other important factors. In addition, the maturity of the transplant center and the expertise of its staff may play a crucial role in patient selection of difficult cases. A high volume, more established transplant center may afford to be able to transplant riskier cases. There are stated universal guidelines; however, there are few hard and fast rules to selection based
on psychosocial criteria. The survey also highlighted that most transplant centers stated that they had some mental health personnel associated with the program to help with psychosocial evaluations: psychiatrists, psychologists, social workers or psychiatric nurses.

As mentioned, active substance abuse and major psychiatric disorders such as schizophrenia and dementia may be absolute contraindications. Other strong relative contraindications include active suicidal ideation, unstable bipolar disorder, gross noncompliance with prior treatment, antisocial personality disorder and no social support. Even the risk of some of these contraindications can be acceptable if there is evidence of long-term stability or a good chance for recovery. For example, a schizophrenic patient who has been stable over a number of years may do perfectly fine with the whole procedure. Approximately one of five people with alcoholic cirrhosis may not fit the criteria for alcohol dependence as will be discussed later. These individuals may have been chronic heavy drinkers who present to transplant centers with cirrhosis being the first major stigmata of their drinking pattern. Individuals who have led stable lives and have good family collaboration may be reasonable risks for transplant without long observational periods. The transplant team itself often functions in crucial roles in psychosocial recovery. For example, an isolated, unemployed man may use the transplant team as a major support system. More difficult to resolve may be the relative contraindications to transplant such as less serious noncompliance, poor social support, problematic personality disorders and the vast array of mood disorders. In addition, you find individuals who aren’t clinically depressed, but seem to have given up the will to live. These patients can be particularly difficult to deal with post-transplant, when effort and rapid participation in rehabilitation is needed to prevent complications. The general goal is short inpatient stays to prevent hospital complications.

**DONOR EVALUATIONS**

Increasingly, transplant programs are exploring the new ways to use live human donors when possible. Obviously this has been a practice with renal transplants for some time due to the fact that most individuals do reasonably well with one remaining kidney. The first successful kidney transplant was done in 1954 when an identical twin brother was used as the source of the kidney. Currently, in addition to kidneys, transplant surgeons now use portions of the liver, lung, heart, and pancreas from living donors.

Several different types of living organ donors have been identified, which include genetically related donors, emotionally related donors, “Good Samaritan donors,” and donors-at-large. Genetically related donors can include first-degree relatives or more distant relatives, while emotionally related donors include spouses, partners, and friends. “Good Samaritan donors” generally refer to people that have no relationship or a distant relationship to the recipient. Finally, donors-at-large have been identified as those who wish to donate an organ in the absence of any
Psychiatric Issues in Organ Transplantation

direct or indirect relationship to the recipient. The number of living donations in recent years has increased due to increasing numbers of individuals needing transplantation and an inadequate supply of cadaver organs. In many Asian cultures, there have traditionally been many more living donor organs used than cadaver organs. This is due to cultural beliefs that include the Confucian tenet of respect for bodily integrity, as well as controversy over the acceptance of a definition for brain death, which limits the availability of cadaver organs.

There have been several factors identified with regards to what motivates people to donate organs. The two most commonly cited reasons for donation include helping to save a family member’s life and improving the donor’s own quality of life. Other factors that have been identified include guilt for past behaviors and concerns about family disapproval or forms of family pressure. It is important to note that all donations should be altruistic and free of any coercion either by family members or the medical team. One ethical dilemma that is currently being debated is whether or not to provide financial incentives for organ donation to help alleviate the organ shortage. Those in favor of financial incentives argue that an increased supply of organs would result in many more lives being saved, which would mitigate any potentially questionable ethical issues. Another potential consequence of financial incentives that has been argued is that the money from the sale of an organ might have a positive impact on the economic well being of donors. The arguments against financial incentives include a departure from American and western society’s ethical standards, the fear of the human body and its parts being treated as commodities, and the potential consequence of exploiting the financial distress of the poor.

Many potential donors are in favor of donating immediately after they learn about the possibility of a living-related transplantation. This is especially true in cases where parents donate to their children. In the situation where parents are donating a part of their liver to a child there is a small risk of complications. In addition, there may also be unrealistic expectations or fantasies that may set parents up for extreme guilt or self-reproach if the donor liver fails. Determining if there are unrealistic expectations and forming an alliance if further support is needed may be the goals of psychiatric referral. However, psychiatric evaluation and follow-up support is essential for all living donors. Important elements that should be included in any donor evaluation include: donor motives and decision-making processes; description of the relationship with the recipient; prior and current beliefs about organ donation; ability to provide informed consent; attitudes of significant others toward decision to donate; availability of support from family and/or friends; past and current psychological problems and treatments; past and current substance use history; any current life stresses; and financial preparations for time off work. The majority of donors do well in terms of psychological adjustment. However, throughout the evaluation process and in follow-up it is critical to keep in mind the well being of the donor and to make sure that physically, emotionally, and financially they will not be at risk for complications.
EMERGENCY EVALUATIONS

There are situations when a decision to transplant is made on an emergency basis. What most likely presents as an emergency situation today is acute liver failure due to toxins such as acetaminophen; however, there are numerous medical conditions that present as acute liver failure. A typical situation might be a young, troubled person who is drinking and decides to take an overdose of acetaminophen. Acetaminophen toxicity itself could cause liver failure; however, alcohol increases the risk due to its increase of toxic metabolites. Treatment is usually effective; however, when it is not, acute liver failure may be fatal without transplantation. More often these patients are already confused, comatose and may rapidly develop increased intracranial pressure. Because of their mental status, it may be impossible to interview them. Often from family you can get a history of depression, personality problems or substance abuse. Sometimes the problems appear out of the blue to the family. In many cases a decision will be made to transplant even in a situations where suicide was a clear intent. Depression is potentially a treatable condition and suicidality might be a transient state. Conversely, in situations where you have young adults who have clear histories of intractable substance abuse or severe antisocial personalities you may decide it is not a reasonable risk. In situations where you decide not to transplant, it is important to clearly inform the family regarding the rationale for the decision and refer to other institutions if possible.

THE DIFFERENTIAL OF COMMON PSYCHIATRIC DISORDERS IN TRANSPLANTATION

The prevalence of psychiatric issues in transplant patients is probably comparable to the prevalence of other serious medical illnesses. However, as we will discuss later differences in end organ damage and their etiologies may make for differences. Baseline psychological factors surrounding suffering from early onset type 1 diabetes mellitus may raise the possibility of different problems in these patients than older cardiac transplant patients. The most common disorders you will encounter in all transplants are delirium, depression, anxiety, adjustment disorders, organic mood and personality disorders, substance abuse and lifelong personality disorders. What often makes diagnosis challenging is the great overlap of psychiatric conditions, personality, culture, and physical symptoms of disease which masquerade as psychological symptoms, medication side effects, staff anxiety and presence of cognitive disorders. Often only good detective work or time clarifies some of these issues. The detective work includes getting good pre-morbid histories and systematically ruling out medical causes and medication side effects. Often no definitive etiology can be ascertained and the cause is unknown or multi-factorial. Even when it is clear what is causing the psychiatric symptoms, some symptoms such as delirium can only be controlled after the medical cause abates: steroid-related mood changes or insomnia secondary to high dose steroid administration.
MOOD DISORDERS

The most common affective symptom that we encounter in the transplant population is depression. Depression is a subjective symptom that can range from mild, transient sadness secondary to a known stressor such as illness, to more serious clinical syndromes such as major depression or bipolar disorder. The most obvious serious medical emergency in depression is suicide. Depression as a symptom is probably not any more common in transplant patients than any other serious life threatening illness. Most transient, sad feelings are appropriate and dealt with in ways that are characteristic for individuals. Depressive symptoms can be the result of the many stressors surrounding the primary disease or other life complications. When they are clearly beyond the severity of what one would reasonably expect and these symptoms do not meet criteria for major depression then the depression is labeled an adjustment disorder, with depressed mood. 30% of post liver donors can experience depression and 2-17% of post-op liver and heart transplant patients meet criteria for major depression. In transplant patients, quiet delirium and transient anxiety can easily be misinterpreted as adjustment disorder with depression. There is a great overlap in prevalence between depression and anxiety disorders. When people have major illness many of the physical symptoms mimic symptoms of depression such as insomnia due to pain or metabolic abnormalities, fatigue due to the primary illness or medications, loss of appetite/

### Table 2. Major depressive episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning, at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

**Note:** Do not include symptoms that are clearly due to a general condition, or mood-incongruent delusions or hallucination.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
   **Note** In children and adolescents, can be irritable mood.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
   **Note** In children, consider failure to make expected weight gains.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
weight loss and concentration/memory problems. In many cases we have to look at the cognitive features of depression such as hopelessness, helplessness, guilt, and poor self-esteem to help make the distinction between illness and depression.

The DSM-IV signs and symptoms of major depression are listed in Table 2. Major depression, as discussed earlier, is only a relative contraindication for transplant. In most cases major depression is a treatable condition, even in the medically ill. We will discuss pharmacological approaches to treatment in a following section. It must be noted however that large scale studies in relatively healthy individuals show that some forms of talking therapies such as cognitive-behavioral or interpersonal therapy can be equally as effective in treating non-melancholic major depressions. Melancholic major depression may be a more psychotherapy resistant, genetic form of the illness. It must be noted, however, that there is no contraindication to using both medications and therapy. This is the most common practice in medical settings. Psychotherapy in transplant patients that are feeling up to it can proceed much like therapy in healthy individuals, especially in post-transplant patients. Transplant issues include guilt, shame, denial, the stress of long waiting periods, unrealistic expectations, complications such as rejection, re-entering the work world and relinquishing family responsibilities. The general mode of therapy is here and now, supports patient’s strengths, and entails active listening, but also involves giving advice and connecting people to resources.

The most commonly used antidepressants used in transplantation medicine are listed in the pharmacology section. SSRIs are indicated for initial treatment. It can take 4-8 weeks to show some signs of improvement. If there is partial improvement the dose can generally be pushed to two to three times the initial dose at weekly intervals. Elderly, the seriously ill and patients with compromised liver metabolism may have to start at half the dose with close monitoring of side effects. Nefazadone and fluvoxamine are relatively contraindicated due to their P450 3A4 interaction with prograf and cyclosporine. Ritalin, a psychostimulant, can be helpful in de-energized, depressed, medically ill patients. Stimulants, if effective, work more rapidly, and increase energy and appetite.

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<th>Table 3. Delirium</th>
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<tbody>
<tr>
<td>A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.</td>
</tr>
<tr>
<td>B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.</td>
</tr>
<tr>
<td>C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.</td>
</tr>
<tr>
<td>D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.</td>
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</table>
DELIRIUM

Delirium is extremely common in the post-operative period of transplant. The DSM IV signs and symptoms are outlined in Table 3. An assessment should be made of associated features such as sleep disturbance, increased or decreased psychomotor activity and labile emotions. Understanding the patient’s pre-morbid baseline is also important. The cardinal features of delirium that help distinguish it from other cognitive disorders include the waxing and waning of symptoms over a 24 hour period, characteristic, but not definitive diffuse slowing on EEG and the fact that it is usually reversible. Common causes of delirium in transplant patients include in no particular order: metabolic disturbances, vascular disturbances, hypoxia from cardiac or pulmonary causes, infection, hepatic or renal failure, drug toxicity, drug or alcohol withdrawal, and endocrinopathies. Hepatic failure produces false CNS neurotransmitters that may play a direct role in hepatic confusion. There is however, no direct correlation between blood ammonia levels and degree of encephalopathy. The immediate clinical implications of delirium include the patient being a danger to him/herself or others and the pain and suffering that can result from hallucinations and delusions. Many times patients do not remember their perceptual disturbances. At other times patients can remember in excruciating detail, frightening delusions post-operatively that are remembered as traumatic experiences. Delirium should be addressed in an appropriate way to minimize suffering. In addition, delirium can be a heralding event of something seriously going wrong in the body. Having a good understanding of current or pre-morbid psychiatric conditions will help with diagnosis. Delirium is a common cause for the patient to be declared incompetent to sign for medical procedures. Management includes coordinated care with all physicians, reviewing history and pertinent laboratory and radiological examinations. Basic tests include CBC with differential, chemistry panels including electrolytes, liver and renal function, arterial gases, EKG, blood cultures V/Q scans, CT and MRI of the brain and other organs and lumbar puncture. Cognitive tests such as trail making tests or digit span can highlight mild cases.

Treatment entails identifying and treating reversible causes of delirium, monitoring safety (patient may often need a sitter or soft restraints), educating patient and family regarding the diagnosis and reassuring that in most cases the delirium is reversible. It is helpful to provide regular reorientation and provide as much familiarity in the environment as possible. One preventive strategy is to have patients bring in pictures and other familiar items from home for long hospital stays. The environment should not be over or under stimulating as either can promote perceptual disturbances and confusion. The ICU, either pre or postoperatively, can be particularly disturbing to patients due to high activity in the unit or the feeling of relative isolation. Somatic interventions can include antipsychotics, droperidal, and benzodiazepines (however they should be avoided in liver failure patients) and cholinergics for people whose delirium is caused by anticholinergics. Haloperidol (Haldol) is a standard antipsychotic medication used in delirium. It can be administrated PO, IM or IV. IV administration has to be pushed slowly (torsades de pointes EKG change is a rare complication), however this administration has the advantage of decreasing the chance of extrapyramidal side effects.
The initial dose is 1-2 mg Q 2-4 hr (0.25-0.5 mg Q4 for elderly patients). Olanzapine (Zyprexa) 2.5 to 20 mg, has increasingly been found to be an effective antipsychotic in delirium. Neuroleptic malignant syndrome, sometimes caused by high dose neuroleptics, presents with the clinical triad of confusion, rigidity with increased CPK, and hyperthermia and is treated by cessation of neuroleptics and dopamine agonists. Inadequately treated pain can also increase anxiety and cause agitation.

**Substance Abuse and Dependence**

Substance abuse disorders have the second highest prevalence of any of the mental health disorders, second only to anxiety disorders. Approximately one out of every ten adults in the general population suffers from consequences of alcohol abuse and one year prevalence of substance abuse is 6.7%. These percentages are even higher among men. Screening for substance abuse is an essential component in the care of any patient. In transplantation, it is even more crucial to fully characterize any substance abuse problems in patients. In this section we will define the core features of substance abuse, discuss the use of screening instruments and cover recent advances in treatment. The special issue of transplanting alcoholics with liver disease will be discussed in the liver transplant section. It is important to realize that although addiction can be characterized as a relapsing disease, it is treatable. Abstinence rates with alcohol dependence over a lifetime approach two thirds of patients. Thus, it is important to have an informed degree of optimism to work successfully with this population. For many patients substance abuse may be in the remote past and it should not greatly bias our decisions. There is strong evidence from longitudinal studies that five years of sobriety corresponds with extremely low rates of return to drinking. In addition to alcohol and illegal drugs, prescription drug abuse and nicotine addiction can be major issues in this population. Chronic pain syndromes can also be a byproduct of years of illness. Concerns regarding pain control in patients that have been on chronic opiates are not an infrequent concern. Obviously, nicotine addiction is a major risk factor for heart and lung disease. Nicotine addiction is also a vexing addiction to address. Nicotine relapse rates exceed cocaine and heroin relapse rates.

The DSM IV diagnosis of psychoactive substance dependence is included in Table 4. The signs and symptoms include symptoms of physical tolerance and withdrawal. The psychosocial sequelae may include impairment of interpersonal relations, employment or self-care. Any individual not in acute pain, exposed to high dose opiates over an extended period of time will develop physical dependence. They will experience withdrawal on cessation. There are two major neurobiological systems involved in addiction. One is the dopaminergic reinforcement system, which is crucial for craving and for the habitual pattern to develop and the other are the systems that cause symptoms of withdrawal. Fear of withdrawal is a major motivation for continued use. The core feature of the psychological addiction is the loss of control over use and the chronic obsessive craving for the substance which can be chronic, episodic and intense. Understanding the process as a disease may help individuals overcome the addictive process and focus on the task of breaking through denial and accepting help.
The gold standard for diagnosis is a clinical interview, where the goal is determining substance abuse patterns, the severity of use and the consequences of use. In addition, co-morbid disorder should be ruled out. There are however, several screens that have been used in the general and medical populations. The best known are the CAGE and the MAST. The CAGE is composed of four questions (1) have you ever thought you should cut back on your drinking, (2) felt annoyed by people criticizing your drinking, (3) felt guilty or bad about your drinking, (4) had a morning eye opener to relieve a hangover or nerves. For gross screening, a positive response to two out the four would warrant further evaluation. In transplant centers a positive response to any of the questions warrants further assessment by a substance abuse expert. The second major screening devise is the Michigan Alcoholism Screening Test (MAST) which is a 25 item self-screening test. There are similar brief screening instruments for drug abuse. In a transplant center, endorsements of any illegal drug at all warrants evaluation by a substance abuse expert.
Determining the amount of use is certainly important as a guide to the severity of the problem, the treatment course and the possible need for detoxification. The recovery process starts with recognition of the problem and often results in physician referral. The actual recovery process uses a variety of support and educational systems such as drug treatment programs and self help groups. Physicians in their role of trusted healers can often make a difference in getting people to break through denial and to seek help. In nicotine addiction all physicians should be familiar with basic counseling techniques and understand the use of the various pharmacological aids such as nicotine gum and patches, bupropion and nicotine inhalers. All physicians should understand the basic principles of detoxification. The general principle is substituting another drug which is cross tolerant to the drug of abuse and slowly weaning it from the system so neuroreceptors have time to readapt. The gold standard treatment of alcohol withdrawal is benzodiazepines, which are relatively safe and prevent the most serious neuropsychiatric complications of withdrawal such as seizures and delirium tremens. The most important steps are recognizing the need for coverage, following signs and symptoms of withdrawal such as vital sign changes, tremors and agitation and adjusting benzodiazepine doses as needed. One excellent tool for monitoring withdrawal symptoms is the CIWA-AR; however, its use in medical patients may be more difficult to interpret due to other conditions that may be mimicking symptoms. Medically ill individuals, however, are at higher risk for severe complications of withdrawal. Long and shorter acting benzodiazepines can be used for these purposes. Shorter acting benzodiazepines are preferred in patients with hepatic dysfunction or in patients that are elderly. A standard detoxification order in liver patients is Lorazepam .5 to 2 mg P.O or I.V. Q.I.D. on day one adjusted up or down based on response and tapered over 3-5 days. Once a patient is in delirium tremens (D.T.’s) the care is supportive with benzodiazepines, neuroleptics, droperidol, opiates, propofol and paralysis all being options to decrease agitation. When D.T.’s seem intractable a switch to a long acting barbiturate like Phenobarbital may be helpful. Newer pharmacological approaches to aid in long term abstinence with drugs include (1) naltrexone for alcohol and opiate addiction, (2) methadone and buprenorphine for opiate addiction, and (3) pending FDA approval approaches such as acamposate for alcohol use. Treatment of the other psychiatric co-morbidity is also crucial for long-term success.

**ADJUSTMENT DISORDERS**

Adjustment disorders defined as a maladaptive reaction to a known stressor are common psychiatric diagnoses in transplant patients. Often the illness itself or complications present as the most likely stressor. The patients also have life problems that don’t necessarily go away when they need a transplant. Maladaptive reactions come in the form of symptoms such as anxiety, depression, behavioral problems, mixed emotions, physical complaints, social withdrawal or general poor functioning. An adjustment disorder may or may not signal the underlying possibility of a more serious psychiatric problem. Usually the symptoms are time limited and cease when the stressor stops. This is not to say that patients do not feel
very symptomatic during this time and need direct intervention. Usually the approach is supportive therapy where stress and feelings are acknowledged and worked through as necessary. Often medications may be helpful for anxiety or sleep.

**ANXIETY**

Anxiety can be thought of as having both physical and mental components. The physical components are often experienced as fight/flight symptoms of motor tension and autonomic hyperactivity such as shortness of breath, palpitations, sweating, nausea and diarrhea. The mental components can be excessive vigilance, worry or frank panic. The differential of anxiety in the medical setting is extensive. The most common medical disorders that present with anxiety are pulmonary processes such as embolus, hyperthyroidism, complex partial seizure, vascular events, hypoglycemia, drug side effects such as steroid psychosis and theophylline for asthma, adrenal disorders and pheochromocytoma. The psychological manifestations of anxiety range from adjustment disorder as stated previously to anxiety disorders such as panic disorder, posttraumatic stress syndrome, generalized anxiety disorder and anxious personality disorders. The most useful approach for mild anxiety symptoms is reassurance when possible and addressing the underlying cause. The anxiety of waiting for transplant is very common but usually patients have the ability to minimize the severity by psychological defenses such as healthy denial, rationalization and intellectualization. These anxieties are usually episodic and transient. Sustained anxiety with extreme worry, panic or chronic insomnia needs psychiatric referral and usually some medications. The most common medications are benzodiazepines for acute anxious mood; SSRI's for panic attacks and a trial of busperone (buspar) for mild, chronic anxiety. It is generally advisable to limit the use of benzodiazepines to acute periods of anxiety to prevent iatrogenic addiction. A typical approach involves an initial dose of Lorazepam 0.5-1 mg PO T.I.D. or Clonazepam 0.5-1 mg PO B.I.D. The incidence of addiction in individuals without previous addictions or high risk factors is uncommon. There are patients who will do better in long term use on low dose benzodiazepines.

Insomnia is a frequent complication of anxiety, depression and the pain and discomfort of medical illness. Several commonly used medications including stimulants can cause insomnia. Patients with hepatic cirrhosis very commonly complain of sleep disturbance as a core feature of their disease. Pharmacological approaches to liver-related insomnia may not be effective in liver patients and benzodiazepines may not be advisable in liver patients. In other patients, sedative-hypnotics such as benzodiazepines and Zolpidem are useful short-term sleep aids. Sedating antidepressants such Trazadone and Mirtazapine in low doses can also be very helpful. Sometimes the sleep disorder may be a part of a primary sleep disorder such as sleep apnea or restless leg syndrome. In all cases you want to teach good sleep hygiene such as avoiding stimulants and exercise at night, going to bed and waking up at a regular schedule and using the bed for and associating the bed with sleep.
PERSONALITY DISORDERS

Personality is a combination of innate temperament and learned character. Hopefully, everyone has a personality or at least personality traits. When personality traits are maladaptive across time and most situations, exist over a lifetime and have significant effects on functioning, then the personality can be considered as a disorder. The personalities of patients can sometimes be very noncontributory to the quality of their care and how we go about treating them. In other situations our patient’s and our own personalities can be crucial to outcome. Recognizing personality traits, being able to minimize miscommunications and distortions, maximizing coping skills of patients and building therapeutic alliances are the tools of a good physician. Patients may be histrionic (dramatic, attention seeking), obsessive (rigid, perfectionists), narcissistic (self-involved, controlling), dependent (demanding, clinging), masochistic (long suffering), schizoid (unsociable) or paranoid (mistrustful, blaming). In most cases these personalities do not get in the way of patient care. There are incidences where you may have a strong reaction to a patient’s personality and feel it is affecting care. The important thing is to be able to take a step back and sort out your own feelings and thoughts. Often patients react to illness in the way that they have reacted to all problems in their lives and often physicians are seen much like other primary caretakers in their lives such as parents or other authority figures. Examples might include a dependent patient who fears abandonment, a histrionic man who is seductive with nurses, a narcissist who devalues the medical staff, or paranoid patient who appears angry and confused. It must be noted that many apparent personality disorders are in reality transient regressive behaviors in response to stress and they are not indicative of long-term problems. What makes some of these issues more pertinent in the transplant population is the seriousness of many situations and the need for good doctor/patient communication and alliance. When you find yourself having very strong emotional reactions to patients or acting out in ways that are not typical for you, then you may be dealing with a patient with a personality disorder. In these cases it is crucial to discuss your feelings with colleagues or get formal psychiatric consultation. Borderline personality disorders sometime only become clearly evident when the staff as a whole realizes that the patient is splitting the staff into all good and all bad caregivers. A true DSM IV antisocial personality is a relative contraindication for transplant. Antisocial personalities have a serious disregard for the feelings of other people. True antisocial personality must be distinguished from people who may interface with the criminal system for other reasons.

NEUROPSYCHIATRIC SIDE EFFECTS OF COMMON TRANSPLANT MEDICATIONS

Table 5 is a list of common transplant medications that have neuropsychiatric effects. It often can be difficult to know the offending agent because drugs frequently are prescribed concurrently. Cyclosporine is a lipophilic polypeptide that is derived from a fungus, Tolypocladium, and has been a mainstay of immunosuppression since 1978. The microemulsion form, Neoral, allows for greater
bioavailability of cyclosporine. Neuropsychiatric side effects include anxiety, headache, tremor, white matter changes, central pontine myelitis, cortical bleeding, ataxia, seizures, disorientation and visual hallucinations. Corticosteroids, such as Prednisone, are associated with anxiety; depression, delirium and mania are generally a dose-related manner. Prednisone doses above 40 mg are associated with higher incidence of steroid psychosis. OKT3 is a monoclonal antibody used for immunosuppression. Delirium, seizures, tremor, cerebral edema, aseptic meningitis and encephalopathy have been reported, even on the first dose. The side effects of Tacrolimus (Prograf), include prominent neurotoxicity, renal dysfunction, increased blood sugars, headache, anxiety, tremor, restless, insomnia, psychoses and parasthesia. The antiviral agent, acyclovir, can cause tremor, confusion, lethargy, depression, seizures, agitation and delirium. Ganciclovir for CMV can cause headache, delirium, seizures and hallucinations. Alpha interferon used for hepatitis C infection can cause anxiety, irritability and most notably serious depression especially in individuals prone to depression. Common antibiotics such as ciprofloxacin, sulfonamides, gentamicin and cefalosporins can cause delirium and hallucinations. Many antibiotics and antifungal agents have been associated with depression. Amphotericin B an antifungal agent is more clearly associated with delirium. There are numerous medications that have some degree of anticholinergic effect. Anticholinergic delirium has the classic picture of increased temperature, red skin and delirium. Many medications that have minimal anticholinergic effects can have a culminative effect when added together.

**PSYCHOTROPIC MEDICATIONS**

Table 6 is a listing of useful psychotropic medications in the transplant setting. Nortriptyline and desipramine are secondary amine tricyclic antidepressants. Tricyclics continue to be as effective as other antidepressants however side effects and high suicide potential have limited their use. Tricyclics are particularly effec-
Liver and Intestinal Transplantation

Antidepressants

<table>
<thead>
<tr>
<th>Tricyclics</th>
<th>Antipsychotics</th>
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<tbody>
<tr>
<td>Nortriptyline 10 mg BID</td>
<td>Haloperidol .5-5 mg BID</td>
</tr>
<tr>
<td>Desipramine 25 mg BID</td>
<td>Olanzapine 10 mg QD</td>
</tr>
<tr>
<td>Amitriptyline 25-50 mg BID</td>
<td>Seroquel 25-50 mg BID</td>
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<table>
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<tr>
<th>SSRIs</th>
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<tbody>
<tr>
<td>Fluoxetine 10-20 mg AM</td>
</tr>
<tr>
<td>Sertraline 25-50 mg AM</td>
</tr>
<tr>
<td>Paroxetine 10 mg HS</td>
</tr>
<tr>
<td>Citalopram 10 mg QD</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Antianxiety/Hypnotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine 10-20 mg AM</td>
</tr>
<tr>
<td>Sertraline 25-50 mg AM</td>
</tr>
<tr>
<td>Citalopram 10 mg QD</td>
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<table>
<thead>
<tr>
<th>Mood Stabilizers</th>
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<tbody>
<tr>
<td>Lithium 600-900 mg QD Divided dose</td>
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Nefazodone and Fluoxamine are not useful medications in a transplant population because of their strong inhibition of 3A4 isozymes. Many of the transplant medications including cyclosporine are metabolized by this isozyme. Ritalin as mentioned earlier can be helpful in de-energized, depressed medical patients who are resistant with concurrent neuropathic pain, as second line antidepressants and in situations where blood levels are helpful. Amitriptyline is a tertiary tricyclic that is highly sedating and has higher anticholinergic effects. It is useful as a pain adjuvant and sleep aid. Selective serotonin reuptake inhibitors (SSRIs) have taken on the role of first line medications for depression due to their favorable side effect profile and safety in overdose. Although they are all equally effective there are differences in the degree of selectivity and interaction with other neurotransmitter systems. Fluoxetine was the first SSRI; it has a fairly long half-life. A long half-life gives you fairly steady state blood levels; however in poor metabolizers the drug could be difficult to clear. Prozac is a fairly potent 2D6 inhibitor and may have clinically significant interactions with other drugs metabolized at this isozyme. Sertraline is a good middle of the road SSRI. Sertraline’s most troublesome clinical side effect is G.I. distress. Paroxetine is a strong 2D6 inhibitor but the half-life is not as long as fluoxetine. Paroxetine has mild anticholinergic effects so it can be initially sedating and it can induce its own metabolism. Citalopram was the newest SSRI to reach the U.S. market although it had been used in Europe for years. Citalopram has essentially no clinically significant drug-drug interactions. Many of the SSRI’s come in sustained release formulations.
need appetite stimulation. Cautions to its use are situations where tachycardia or lowered seizure threshold is to be avoided. Bupropion, a dopamine agonist, may be particularly helpful in patients who need a more stimulant effect or with patients who are trying not to smoke cigarettes. Trazodone is probably not an effective antidepressant, but it is very useful in the medical setting for sedation to help with insomnia or anxiety. Venlafaxine is both a serotonin reuptake inhibitor and a norepinephrine reuptake inhibitor. At low dose it is essentially a serotonin reuptake inhibitor. Venlafaxine may be useful as a medication to try when a SSRI fails. Mitazapine is a designer drug that selectively blocks some serotonin subtype receptors that cause nausea, agitation and sexual dysfunction. Mitazapine at lower doses can be sedating and help with quick relief of insomnia.

The antipsychotics used in delirium have been highlighted previously. Haloperidol is still the most widely used antipsychotic in medical settings. The newer atypical antipsychotics such as risperidone, olanzepine and seroquel have shown promise in decreasing extrapyramidal symptoms and treating the negative/blunted affect of psychotic disorders. Risperidone does have extrapyramidal effects at higher doses and reduced clearance with liver disease, olanzepine can cause greater weight gain and sedation with chronic use and seroquel requires multiple dosing and is associated with sedation and postural hypotension. Seroquel is also metabolized by 3A4 and may interact with transplant medications.

Lorazepam and oxzepam are relatively short acting benzodiazepines and alprazolam is intermediate. Clonazepam, diazepam and chlordiazepoxide are useful, longer acting benzodiazepines that should be avoided in patients with poor hepatic function or poor perfusion. Busipirone is a sometimes useful anti-anxiety medication for people with generalized anxiety. It is not useful in the short term as it can take up to 3-4 weeks to show effects. Zolidem is a very useful sedative/hypnotic that has some associated abuse potential.

Mood stabilizers have been found to be useful in a variety of psychiatric conditions. The classic indication is for bipolar or manic-depressive illness. Lithium may be particularly useful for long term stability. Levels must be watched closely in patients with body fluid fluctuations. Dialproex Sodium (Depakote) has become a first line treatment for acute mania and mixed bipolar disorders. Depakote may increase ammonia levels in liver cirrhosis. Neurotonin and lamictal are better tolerated in liver patients. Carbamazepine is a mood stabilizer where liver function tests must be watched closely.

SPECIAL ISSUES IN ORGAN TRANSPLANTATION

LIVER TRANSPLANTATION

The most salient psychosocial issue and controversy in liver transplantation is the transplantation of patients with alcoholic liver cirrhosis. There is slowly emerging data on the most important questions initially asked about liver transplantation in alcoholics. These scientific questions have always existed in the context of the larger questions of ethics, moralization and the reality of public perception. The scientific questions have been about survival, return to drinking and quality of life. The ethical question goes as follows: if we have a scarce resource like donor
livers should we allow alcoholics who presumably shoulder a greater responsibility for their illness to receive equal consideration for transplantation? The fact is that alcohol cirrhosis and recently hepatitis C, which in some cases is the consequence of IV drug abuse, are the most common causes for cirrhosis. As the waiting lists rise, it will be important to have data to support the rationale in transplantation individuals who suffer from alcoholism.

First, is the survival of the alcoholic equal to other transplant patients? The answer in both the short and long term is yes. Second, does the quality of life in post-transplant alcoholics look similar to other transplants? Again, the answer is yes. In fact, an otherwise healthy alcoholic recipient can have much less post-transplant morbidity than older or sicker patients. The third question involves the issue of a return to drinking. The data suggests that carefully screened alcoholics have a low return to drinking. Recent data suggest that approximately 13% of alcoholics return to some level of drinking in one year. It is important to note that this is any drinking at all. Most centers can only cite less than a handful of transplanted alcoholics that have run into serious medical consequences from return to drinking. The return to drinking in alcoholic transplants is considerably lower than in non-alcohol related transplanted patients. Three year post transplant data suggests that as time goes on a greater percentage, approximately a third of alcoholics will pick up a drink again. The long term follow up of this cohort is important. The attention now has shifted to how to best select suitable candidates for transplant. The initial approach was to use length of sobriety as a predictor of return to drinking. As mentioned previously, five years of sobriety in general alcoholic populations is correlated with extremely low return to drinking. In the transplant population, most patients have been sober less than five years. One initial study suggested that six months of sobriety might be a reasonable predictor for return to drinking. Although there has been some data that supported that conclusion, the bulk of research has not been able to demonstrate six months as a gold standard. What is probably more important is the severity of alcoholism, the number of failed treatment attempts in the past, other psychiatric co-morbidity including drug use, willingness to enter treatment, follow through and having a sober, supportive home environment. Refer to Figure 1 as a suggested algorithm in assessing alcoholics for transplant. One exception may be the poly-substance abuser, which has been shown in some series to be associated with poorer outcomes. With long wait times most programs have a chance to put patients through the test of compliance. There are obviously no guarantees as people can and do return to drinking when they feel well again. However, the reality is that liver transplantation is associated with a low incidence of relapse compared to the 60% relapse in three months in natural circumstances.

**Kidney**

Renal failure can be very devastating to a person's quality of life, even if the renal failure can be managed reasonably well medically with dialysis. For many patients who have dialysis complications or whose quality of life or life span is compromised by dialysis, a renal transplant is a reasonable option. The pre-selection process should screen patients like any other transplant and select individuals who
are going to take care of their graft, whether they receive it from a live or cadaver donor. Due to the high numbers of kidney patients on transplant lists, it is often not feasible to do a psychiatric screening of all of them. However, if a patient has been on dialysis, psychosocial assessments can often be obtained from a patient's dialysis unit. Kidney recipients can wait long periods, with little direct contact with the transplant team and suddenly get “beeped” for a transplant. This
Fig. 1B. Pretransplant alcohol-dependence assessment II. From Beresford et al. A Rational Approach to Liver Transplantation Psychosomatics. 31(3):241-254. Reproduced with permission.
uncertainty of “when” can generate anxiety. The most common problem seen by mental health personnel is post-transplant patients who stop taking their medications and reject their organ. Many times these patients want to be re-listed for another transplant. Reasons for noncompliance range from denial, lack of insight, finances (patients need to stay on top of funding sources for transplant medications by contacting their social worker), chaotic lifestyles, personality disorders and other mental problems. Also, these patients may be suffering from medical consequences of their primary disease. Only with very careful evaluation and demonstration by the patient that poor self-care is clearly behind them would one consider re-transplantation.

KIDNEY/PANCREAS
These patients are distinguishable by the fact that they most often have a history of being brittle diabetics from childhood. The dynamics of having an early, unpredictable and often dramatic chronic disease can interfere with normal separation/individuation and emotional development in some patients. Many of these patients have underlying low self-esteem and issues of control with authority figures like parents and physicians. Some are and will continue to have to deal with other end organ damage like retinal hemorrhage and neuropathy. Quality of life series suggest that this group may have a more protracted recovery period before their quality of life changes. Frequently it may be up to a year before patients really see the positive risk/benefit to the surgery. It is important to express hope that the procedure will arrest the disease process, but not to oversell the procedure to the point that patients are not prepared for complications.

HEART, LUNG TRANSPLANTS
Many of these patients have history of depressive disorders, anxiety and substance abuse. Heart and lung transplants also can raise ethical concerns of transplanting patients who may have had knowledge that their alcohol or smoking could contribute to disease. Heart and lung failure patients can have such impaired quality of life and low survival rates that transplant is the only option. The selection process with these patients is conducted with the same general principles as described above.

CONCLUSION
Consideration of psychosocial issues in transplant is crucial to the good care of these patients. There continues to be areas of needed research. The care of these patients requires a true multidisciplinary approach with nurses, doctors, social workers, ethicists, mental health and substance abuse experts. Understanding of the basic psychosocial issues is important for all staff involved in the care of these patients.

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