

application of Pert's findings and their implications for transplantation are merely speculation at this time but raise some interesting and potentially serious psychosocial and legal issues.

For example, many organ recipients report frequent dreams or nightmares. It is not uncommon to have dreams while they are half awake; sometimes disorientation accompanies sleep disturbance or waking dreams commonly labeled delirium or confusion. Others report changes in temperament or mood, sexual libido, food preferences, and personal preferences. The exact etiology of these perceived changes remains unknown; previously, the dreams and dreamlike disturbances have been attributed to postoperative sleep disruption (e.g., anyone waking up often in the night is more likely to remember more dreams) or considered an unpleasant side effect of the medications (cyclosporine, prednisone).

Other researchers suggest that it is reasonable to include the impact of depression, and possibly other psychologic states, among factors that may affect the net state of immunosuppression in transplant recipients.¹⁷¹

New knowledge within the field of psychoneuroimmunology combined with many more case reports of altered dreams, thought processes, memories, and behavior as the number of organ transplants increases may bring to light new understanding of transplantation psychoneuroimmunology in the decade ahead. One of the first carefully documented and published reports to explore this type of phenomenon may be of interest to readers.²⁹⁹

POSTTRANSPLANT COMPLICATIONS

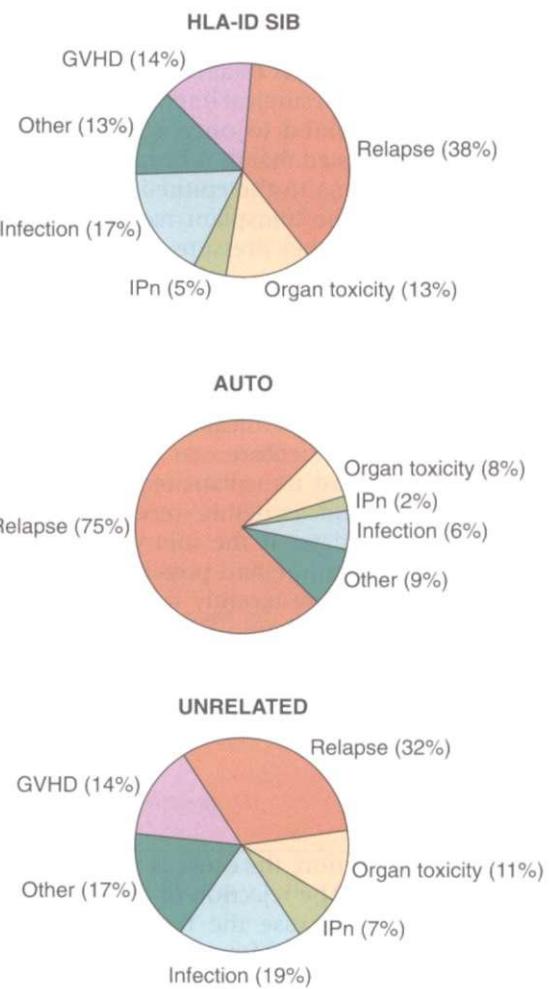
With advances in technology and immunology, transplantation of almost any tissue is feasible, but the clinical use of transplantation to remedy disease is still limited for many organ systems because of the rejection reaction and other posttransplant complications.

Complications following organ transplantation can be classified into three broad categories: (1) complications associated with the procurement and surgical procedure, (2) complications of the transplantation, and (3) complications of the immunosuppressive agents used to prevent rejection. Each type of organ transplantation has its own accompanying surgical risks and complications (see discussion in each section).

Following surgery, two main complications of organ transplantation remain infection and organ rejection. The most serious posttransplant complication is death, which can be caused by a infection, organ toxicity, GVHD, relapse, and various other causes (Fig. 21-5).

Infection and organ rejection are common and treatable, but prevention is the first step. For this reason, pretransplantation serologic testing is done to determine histocompatibility and to avoid transmitting infectious agents (e.g., CMV, vancomycin-resistant enterococci [VRE], HBV, HCV) from donor to recipient. Herpeszoster infection can be a serious complication of organ transplantation, with postherpetic neuralgia occurring in almost half of the recipients affected. Heart and lung

Causes of Death after Transplants Done in 1998-2002



Key:
 HLA-ID SIB = Human Leukocyte Antigen-Identical Sibling
 GVHD = Graft Versus Host Disease
 IPn = Interstitial Pneumonia

Figure 21-5

Causes of death after transplants done from 1998 to 2002. (Courtesy Center for International Blood & Marrow Transplant Research [CIBMTR]. CIBMTR Newsletter 12[1], May 2006.)

recipients have the highest incidence (15%), followed by renal (7.4%) and liver (5.7%).¹¹⁷

As the survival rates improve other complications arise, such as the increase risk of other diseases such as cancer and diabetes.

Ischemic Reperfusion Injury

Ischemic reperfusion injury may occur with any organ transplantation; it results in the onset of the inflammatory response, which has both immediate and long-term effects on the donated organ. The donated organ is very sensitive to the amount of time it is not being perfused or supplied with blood, which can lead to ischemia.⁶²

The presence of ischemia can result in permeability of the endothelium and activation of many inflammatory-associated cells, such as macrophages and neutrophils. The endothelium loses its antiadhesive nature and a thrombogenic environment is established.³⁴

After the organ has been surgically implanted, the clamps are removed to allow blood to once again perfuse the organ. It has been suggested that the abrupt flow of blood may create further trauma to the epithelial lining of the blood vessels because the transplant recipients may be circulating blood at a higher pressure than to what the donor organ is accustomed.

This phenomenon is especially common in heart or lung transplantation in the presence of comorbid pulmonary hypertension. This results in a reperfusion injury, which leads to leukocytes and platelet aggregation, which further causes endothelial permeability and inflammatory cell activation and adherence.

It is common for most transplant recipients to have to recover from a mild ischemic reperfusion injury usually lasting 3 to 5 days. If the injury is significant, organ dysfunction and failure and possible death of the recipient are possible. More recently it has been shown that there is a significant relation between the presence of an ischemic reperfusion injury and development of chronic rejection via the activation of both the innate and adaptive immune responses and organ regeneration.³⁴

Histocompatibility

In all cases of graft rejection, the cause is incompatibility of cell surface antigens. The rejection of foreign or transplanted tissue occurs because the recipient's immune system recognizes that the surface HLA proteins of the donor's tissue are different from the recipient's.

Certain antigens are more important than others for successful transplantation, including ABO and Rh antigens present on red blood cells and histocompatibility antigens, most importantly the HLA. As expected, there is a better chance of graft acceptance with syngeneic or autologous transplants because the cell surface antigens are identical. For all categories of transplantation, minimizing HLA mismatches is associated with a significantly lower risk of graft loss.⁶⁰

It has been shown that in a person with HLA antibodies, the antibodies are directed against the antigen of the donor kidney and will result in immediate graft failure. It has also been documented that when specific HLA antibodies are directed against B cells, hyperacute rejection is produced, leading to graft dysfunction and possible failure.³⁰²

Rh antigen is more important in heart and kidney transplants than in lung transplantation. In renal transplants HLA cross-matches are routinely performed, whereas this is not commonly done in lungs (unless the candidate has a high patent reactive antibody count). Cross-matching policies may vary by institution.

The process of determining histocompatibility, that is, finding compatible donors and candidates, is called *tissue typing*. Before transplantation, testing in the laboratory is carried out to determine whether antibodies incompati-

ble with the donor have been formed by the candidate (a positive cross-match). If the cross-match is positive, the transplant will fail; a negative test result is necessary for a successful transplant.

Graft Rejection

Transplant rejection may occur for immunologic or non-immunologic reasons. When the body recognizes the donor tissue as nonself and attempts to destroy the tissue shortly after transplantation, rejection occurs as an immunologic phenomenon primarily because of histocompatibility.

Nonimmunologic factors can occur as a result of the draining reperfusion process necessary in organ harvest and transplantation. Ischemic injury occurs when normal blood and oxygen supply to the donor organ is stopped at the time of organ harvest, whereas reperfusion injury can occur when blood flow is returned to the organ after transplantation. Ischemic reperfusion injury has been associated with an increase in acute and chronic rejection.³⁴

As residual blood is drained from the transplanted organ into the host's general circulation, the body recognizes the transplanted tissue cells as foreign invaders (antigens) and immediately sets up an immune response by producing antibodies. These antibodies are capable of inhibiting metabolism of the cells within the transplanted organ and eventually actively causing their destruction.

Research to develop a reliable method to reduce the ischemic reperfusion injury is currently ongoing. Eliminating the occurrence of poor early graft function and consequently reducing the chances for rejection episodes are the primary goals of these investigations.^{81,84}

Types of Graft Rejection

There are three types of transplant rejection—the hyperacute rejection, the acute or late acute rejection, and the chronic rejection—depending on the amount of time that passes between transplantation and rejection (Table 21-3).

Hyperacute rejection (rare with antibody screening and tissue typing) is dominantly mediated by humoral responses of the immune system (natural antibodies, complement cascade) and the activation of coagulation factors. There is an immediate rejection after transplantation when the recipient has preformed antibodies to donor tissue.

This reaction necessitates prompt medical action, which may include surgical removal of the transplanted tissue or the use of life-support devices such as a temporary ventricular assist device (VAD) or extracorporeal membrane oxygenator, in the case of a heart or lung transplantation. These devices can be used to support blood circulation and gas exchange while the patient undergoes such treatment as plasmapheresis and immunoglobulin therapy in an attempt to remove the reactive antibodies. Medical treatment may diminish the hyperacute rejection response and allow the donor organ to recover, or it may allow time for another donor organ to be implanted.¹⁹⁰

Table 21-3 Clinical Manifestations of Organ Rejection

Hyperacute Rejection	Acute (Late) Rejection	Chronic Rejection
Immediate reaction Severe graft dysfunction or failure, then death Death	Occurs days to years after transplantation May be asymptomatic in early stages Fever, constitutional symptoms (flu-like) Loss of appetite Graft tenderness Blood pressure changes Dyspnea Fatigue Peripheral edema, weight gain Inflamed skin lesions Reduced exercise capacity <i>Organ-related symptoms</i> Kidney: Proteinuria, uremia, neurologic symptoms, nausea and vomiting Liver: Palpable liver, jaundice, hematemesis (vomiting blood), abdominal pain, ascites, neurologic symptoms (see Box 21-8), elevated transaminase, elevated bilirubin Heart: S3 gallop, arrhythmias, jugular vein distention Lung: Changes in respiratory status, breathlessness, prolonged need for ventilatory support, fall in spirometric values (>10% change/reduction from baseline; <90% at rest), decreased FEV ₁ >10%, dry or productive cough, change in sputum (color, amount), decreased oxygen saturation, reduced vital capacity; decreased exercise capacity, radiographic changes Pancreas: Nausea, vomiting, anorexia, other gastrointestinal symptoms, urologic symptoms	Occurs 3 months to years after transplantation May be asymptomatic in early stages Organ-related symptoms Histologic changes Graft dysfunction Graft failure

The *acute* or *late acute rejection* can appear days to years after the transplantation. This type of rejection involves a combination of cellular and humoral reactions. Acute antibody-mediated rejection or vascular rejection typically occurs days to weeks posttransplant. There is an interaction between the recipient's antibody and donor HLA or endothelial cell antigens that leads to graft vessel injury and thrombosis formation. Acute cellular rejection is most common in the first 3 to 6 months posttransplant and involves the proliferation and infiltration of T lymphocytes and macrophages.^{134,190} Despite the early pattern of acute rejection, both humoral and cellular rejection can occur at any time.

Clinically, there is sudden onset of organ-related symptoms, which may be associated with fever and graft tenderness, fatigue, or decrease exertional tolerance, or the recipient may be totally asymptomatic. Graft rejection must be differentiated from immunosuppressive toxicity.

This form of rejection can be reliably graded using a system of categories of mild, moderate, and severe rejection. Acute rejection, if detected in its early stages, can be reversed with immunosuppressive therapy. With the advancement in immunosuppressive medications and management, there has been a decline in acute rejection, which has lead to an increase in 1-year graft and recipient survival.³¹⁶

Chronic rejection can occur as early as 3 months, but it is usually months to years before the chronic rejection occurs. This type of rejection develops as a function of both cell-mediated and humoral-mediated reactions and is characterized by slow, progressive organ failure.

Growing evidence indicates that chronic rejection is the aggregate sum of irreversible immunologic and non-immunologic injuries to the graft over time. Chronic rejection is associated with chronic vascular changes such as arteriopathy or diffuse atherosclerosis with intimal proliferative changes depending on the type of organ. In the presence of a chronic immune/inflammatory process within the donor organ, the intimal lining of the vascular tissue undergoes fibrosis and vascular remodeling. This leads to a decrease in the lumen size and ischemia of the distal tissue and perpetuates the inflammatory reaction.^{126,190}

A history of acute rejection episodes, either asymptomatic or clinically apparent, and inadequate therapeutic level of the immunosuppression medications or poor compliance are among the most recognizable immunologic risk factors for chronic rejection.²¹⁸

Adherence to immunosuppressive therapy is a key factor contributing to transplant failures that occur within 2 years after surgery. Financial barriers such as the lack of insurance coverage are the most common reason for non-compliance. The Immunosuppressive Medications Act

supported by the National Kidney Foundation would extend Medicare coverage of postoperative medications so that organs are not lost because of a lack of insurance coverage.²²⁷ Chronic rejection results in irreversible cellular damage within the donor organ and leads to graft dysfunction and eventually failure.^{126,190} Rarely is chronic rejection responsive to medical therapies.

Graft-Versus-Host Disease

Acute GVHD remains a major obstacle in the curative potential of allogeneic stem cell or organ transplantation. The use of BMT to bone marrow-depleted or immunodeficient people has resulted in the complication of GVHD. People at highest risk include premature infants and others who are immunosuppressed as a result of either congenital or acquired disease or because of the administration of immunosuppressive therapy, as in the case of organ transplant recipients.

GVHD occurs when immunocompetent T lymphocytes in the grafted material recognize foreign antigens in the recipient, initiating a cascade of events mediated by cellular and inflammatory factors and resulting in a reaction against the recipient's tissues.⁹⁷ GVHD may be acute, occurring in the first 1 to 2 months after transplantation, or chronic, developing at least 2 to 3 months after transplantation.

GVHD remains the major toxicity of BMT. It does not occur in autologous BMT or peripheral blood stem cell transplantation (PBSCT) but may occur in an allograft or syngeneic transplant, even with a perfect HLA match, because of unidentified and therefore unmatched antigens. Pretransplant immunologic and genetic manipulation using hematopoietic stem cells has minimized GVHD in individuals receiving high-dose chemotherapy.

Key risk factors for the development of GVHD include older age, source of allogeneic stem cells (marrow vs. blood), and gender mismatching. Conditioning regimens containing total body irradiation are associated with higher incidence and severity of GVHD compared with those involving only chemotherapy.⁷

Signs and symptoms of GVHD are fever, skin rash, hepatitis, diarrhea, abdominal pain, ileus, vomiting, and weight loss. As the disease worsens, the skin rash may progress to skin blistering with severe diarrhea, abdominal pain, and hepatic dysfunction.

Chronic GVHD is also characterized by hardening of organ tissues (connective tissue disorders such as scleroderma) and drying of mucous membranes (mucositis), especially in the gastrointestinal mucosa, liver, respiratory bronchioles (bronchiolitis), and skin (scleroderma or systemic lupus erythematosus) (Box 21-7).

A generalized polyneuropathy coincident with the occurrence of GVHD has been reported. The neuropathy affects proximal and distal muscles and demonstrates hyporeflexia or areflexia. Electrophysiologic studies do not meet strict criteria for demyelination. The signs of neuropathy improve after immunosuppressive treatment or simultaneously with the resolution of GVHD.

Preventing GVHD through the use of prophylactic (cyclosporine or tacrolimus) is advised when appropri-

Box 21-7

SIGNS AND SYMPTOMS OF GRAFT-VERSUS-HOST DISEASE

Gastrointestinal

- Mucositis
- Esophageal inflammatory changes
- Abdominal cramping
- Diarrhea
- Anorexia
- Ileus
- Hepatic injury (hepatitis)

Pulmonary

- Bronchiolitis

Integumentary

- Hypopigmentation or hyperpigmentation of the skin
- Progressive maculopapular rash
- Sclerodermatous changes
- Pressure ulcer formation
- Alopecia
- Photosensitivity
- Keratoconjunctival sicca

Neuromusculoskeletal

- Generalized polyneuropathy
- Muscle wasting and weakness
- Joint contractures (chronic GVHD)
- Changes in deep tendon reflexes (hyporeflexia or areflexia)
- Guillain-Barré syndrome (rare)
- Polymyositis (rare)

Other

- Hemorrhage
- Infection

ate. Untreated GVHD is often fatal as a result of hemorrhage and infection. Inhibition of cytotoxic T-lymphocyte-mediated tissue injury in the early stages of GVHD is recommended along with administration of agents to eliminate the donor's lymphocytes.

High-dose corticosteroids are the mainstay of therapy. Treatment with immunosuppressive therapy including prednisone, cyclosporine, or tacrolimus (FK506, Prograf), thalidomide, or a combination of these agents has improved the long-term outlook for people with chronic GVHD. Even so, the overall fatality rate is about 20%; in the severe form, this rate exceeds 80%. Most people with grade 4 disease do not survive.⁷ Chronic GVHD may resolve slowly (sometimes taking years) with gradual restoration of cell-mediated and humoral immunity function.

Immunosuppression

The fact that a primary role of the immune system is to distinguish between self and nonself presents a major problem for the transplant recipient: the immunologic response of the recipient to the donor's tissues. In the person with an intact immune system (immunocompetence), the recipient's immune system recognizes

the transplanted tissue or organ as foreign (nonself) and produces antibodies and sensitized lymphocytes against it.

The ultimate objective of immunosuppressive therapy (see the section on Medications under Advances and Research in Transplantation in this chapter) is to block transplantation candidate reactivity to the donor's organ while sparing other responses. Since these drugs suppress immunologic reactions, infection is a leading cause of death, particularly within the first postoperative year.¹⁹² Infection is still the leading cause of death in some transplant recipients. However, increased understanding of rejection mechanisms has made it possible to suppress specific elements of the immune response and has led to a decrease in death-related infection and rejection.^{30,316}

Although lower amounts of immunosuppressive drugs are now prescribed, these drugs must be taken for the life of the recipient and physical changes (see Figs. 11-5 to 11-7) and other side effects remain a well-known problem (see Table 5-3).

Side Effects of Long-Term Immunosuppression

Long-term immunosuppression can have serious consequences for the recipient, such as diabetes and accelerated hyperlipidemia, with associated atherosclerosis and subsequent cardiovascular disease.

There is a high incidence of musculoskeletal effects that will concern the therapist, such as decreased bone density and osteoporosis. Half of all transplant recipients are diagnosed with osteoporosis and one third have documented vertebral fractures,¹⁹³ steroid-induced myopathies, as well as avascular necrosis and musculoskeletal injuries.

Within the first 6 months after transplantation, the organ candidate can lose more bone density than any woman during the postmenopausal period. Osteoporosis has become a silent contributor to mortality in organ transplantation.²⁸⁶ Physical therapy intervention must address this concern.

Neurotoxic reactions are manifested by a fine tremor, paresthesias, and occasionally seizures. Sensorimotor demyelinating polyradiculoneuropathy has been reported as a rare side effect in liver transplant recipients receiving tacrolimus (Prograf, FK506).¹⁹⁵ Neuropathies and paresthesia can occur with FK506³³⁵; quadriplegia is a rare adverse event.

The individual may report difficulty completing fine motor activities of daily living (ADLs), such as poor handwriting and difficulty eating. These changes may be significant enough to stop some people from going out publicly or dining out in restaurants. Reports of memory loss may not be secondary to actual alterations in memory, but rather a decrease in executive function.^{69,293} Most of these events are dose related and reversible.

Cancers in Solid-Organ Transplant Recipients

Organ recipients have three times the incidence of various cancers, and some specific cancers are 100 times more frequent in the immunosuppressed population after transplantation than in the general population. Cancer incidence is proportional to immunosuppression drug

levels.⁷² Cardiac transplant recipients have a higher incidence of cancer than do other transplant recipients, perhaps because of the higher levels of immunosuppression.

The most common tumors among transplant recipients (40% to 50% incidence) are squamous cell cancers of the lips and skin owing to the enhanced photosensitivity. Squamous cell carcinoma is often more aggressive than in nonimmunosuppressed people, with multiple sites of presentation and frequent recurrence.⁹³

Skin cancers involving papillomavirus are the most frequent cancers observed in transplant recipients, occurring in half of the long-term survivors. The incidence of basal cell carcinoma is 10% higher than the general population, and the incidence of squamous cell carcinoma has been reported to be 250 times greater in orthotopic homologous transplantation recipients.¹⁴⁸

Organ recipients are also at increased risk for some malignancies such as Kaposi's sarcoma, non-Hodgkin lymphomas and other posttransplant lymphoproliferative disorders, soft tissue sarcomas, carcinomas of the vulva and perineum, carcinomas of the kidney, and hepatobiliary tumors.^{74,309}

True incidence of cancer is difficult to determine given the different organ types being transplanted and inconsistent reporting to cancer registries. Most transplant recipients, however, have no increased risk of most cancers common in the general population, such as lung, breast, prostate, or cervical cancers. An increased risk for colon cancer remains controversial.³¹¹

Cancer is more common in those receiving kidney transplants than in the general population and more common than in comparable patients on dialysis. Malignant lymphomas occur 11.8 times more often in kidney transplant recipients compared with the general population. The majority of lymphomas occur after the first posttransplant year.²³⁵

It has been suggested that immunosuppressive agents may cause DNA damage and interfere with normal DNA repair mechanisms. Immune surveillance, which ordinarily prevents the growth and development of malignancies, may be impaired by certain immunosuppressive medications. Exactly why kidney transplantation is more affected by these factors than other organs remains unknown.¹⁶¹

There have been studies that have reported an increase in lung cancer in heart transplant recipients who have a history of smoking. There is an increased incidence in posttransplant lymphoproliferative disease in heart transplant recipients who underwent OKT, induction therapy or use of antithymocyte globulin for rejection therapy.

Gastrointestinal Problems

Gastrointestinal complications of solid-organ transplantation have been well described in the literature. Disorders of the colon and rectum are a considerable source of morbidity, especially after heart and lung transplantation. Colorectal problems occur among 7% of lung transplant recipients, 6% of heart-lung transplant recipients, and 4% of heart transplant recipients. Major events include diverticulitis, perforation, and malignancy. More

minor complications include polyps, pseudo-obstruction, and benign anorectal disease.¹¹³

Wound Healing

Advances in surgical techniques and immunosuppression have led to an appreciable reduction in postoperative complications following transplantation. However, wound complications as one of the most common types of posttransplantation surgical complications can still limit these improved outcomes and result in prolonged hospitalization, hospital readmission, and reoperation.²¹⁰

Chronic immunosuppressive drug therapy impairs and prolongs wound healing, especially common among those organ recipients with diabetic or neuropathic pedal ulcers. The two most important risk factors for wound complications are immunosuppression and obesity. Other risk factors include surgical and/or technical factors (e.g., type of incision, reoperation, surgeon's expertise), advancing age, diabetes mellitus, malnutrition, and uremia.²¹⁰

Therapists should be involved in preventive management of wound complications; identifying and minimizing risk factors whenever possible is important. Therapists involved in wound therapy should inform their clients, members of the clients' families, employers of clients, and third-party payers to expect longer times in healing plantar ulcers because of long-term immunosuppressive therapy.²⁸⁰

Total-contact casting remains a highly effective and rapid method of healing neuropathic pedal ulcers in diabetic immunosuppressed clients and transplant recipients, although it may take several weeks longer than it would for those individuals who were not immunocompromised. Transplant recipients who are immunocompromised appear to be no more at risk for wound failure complications when using total-contact casting as a treatment modality than those individuals without these additional variables.²⁸⁰

ORGAN TRANSPLANTATION AND EXERCISE, ACTIVITY, AND SPORTS

Whereas some people will have a period of only a few days of physical inactivity before transplantation (e.g., toxic liver failure), the majority of organ candidates will live with their diseased organs for a prolonged period of time, often years. By the time of organ transplantation, candidates usually have experienced a period of long-term ill health leading to end-stage organ failure accompanied by severe deconditioning and exercise intolerance.

Complications of long-term immunosuppressive therapy and the kind of organ that has failed will determine some of the problems an individual may face in relation to exercise, activities, and sports. Most transplantation candidates experience an impaired physical performance level that not only interferes with the ability to perform leisure-time exercise, but also often limits the ability to perform even simple physical tasks, such as climbing stairs.¹⁷⁰

Weakness, dyspnea on exertion, and fatigue are often present, and there may be little motivation for exercise and sport. Finding an activity or exercise that the person can do successfully is the first step to initiating regular lifelong exercise.

Whether or not a potential candidate receives a transplant, therapy can be focused toward more function and improved quality of life. Exercise training increases work capacity as measured by increased oxygen consumption ($V\text{O}_{\text{2}}$), increases efficiency of oxygen utilization in the muscles, normalizes distribution of muscle fiber types, increases aerobic metabolism with delays in the onset of lactic acid buildup, and promotes modulation of the parasympathetic nervous system with more sensitive baroreceptors.^{36,246} Exercise training also improves psychologic factors such as depression in pretransplant and posttransplant individuals.^{57,178,246}

An assessment of transplant candidates must take into consideration daily life and daily activities, including potential return to work requirements. For example, a job that requires lifting requires assessment of cardiovascular compliance and hemodynamic stability during lifting, whereas someone at home must be safe in ADLs.

Pretransplant Activity and Exercise

It has been proposed that peripheral skeletal and respiratory (in the case of thoracic involvement) muscle work capacity is reduced before transplantation and contributes to the limitations of exercise seen in the posttransplantation population.³²⁹ Preservation of muscle strength before transplantation becomes impossible for some who are acutely ill. Muscular dysfunction attributable to detraining and deconditioning is common.¹⁸¹

While an individual waits on the transplant list, it is important that the candidate participate in an exercise program with the goal to promote functional mobility. Exercise programs should be individualized to focus on the needs of each person required to maintain function, self-control, and esteem.

Exercises should be functional, with an emphasis on strengthening the proximal muscles of the pelvis and the lower extremities, especially the gluteal and quadriceps muscles, as well as muscles of the shoulder girdle and trunk to support upper extremity function and accessory respiratory efficiency.

Weight training to maintain or increase muscular strength may help the candidate counteract the steroid's targeting effects on muscle and adverse effects of immobility and chronic inflammatory effects.^{64,233,246} It has been reported by transplantation centers around the United States that transplantation candidates who take part in an exercise program before surgery are likely to recover more rapidly following transplantation. Researchers are beginning to publish data on exercise performance before and after transplantation.^{26,58,125,250}

Posttransplant Activity and Exercise

After organ transplantation, the underlying pathophysiologic process returns to normal if the donor organ is functioning appropriately. For example, exercise perfor-

mance in individuals with heart transplants increases with respect to pretransplantation performance but remains subnormal and does not improve with time after surgery.²⁶ The extent of recovery depends on the function of the transplanted organ, which in turn is determined by the quality and function of the organ implanted, the presence of any rejection or infection, and the development of other comorbidities.

Despite the pretransplant physical deconditioning and exercise limitations, transplant recipients can progressively return to a normal life with return to work and even safely participate in sporting activity and exercise.¹⁷⁰ National and International Transplant Games, a multi-disciplinary sporting event started in 1978, illustrates the degree to which organ candidates can return to exercise and sports. At the 2006 National Kidney Foundation sponsored games in Louisville, Ky., transplant recipients from all 50 states, with the oldest recipient being 84 years of age, participated to celebrate the gift of life and experience competition.

Regular exercise enhances quality of life and lowers the risk of cardiovascular disease, hypertension, and diabetes. This is especially important in transplant recipients because many immunosuppressive drugs can be atherogenic and diabetogenic.^{120,166,333} Standards for how soon after transplantation physical training can or should begin have not been uniformly established. It is recommended that physical therapy should begin on postoperative day 1, with the goal to mobilize out of bed as soon as medically stable. Physical training should begin as soon as the recipient is up and walking.

Despite the restoration of system function that allows most transplant recipients to return to an improved quality of life, including returning to work, having and caring for children, and participating in leisure recreational activities, a persistent limitation in peak aerobic and anaerobic capacity can be appreciated when compared with health- and age-matched normal subjects.³²⁹

There is a decrease in maximal and peak oxygen consumption (V_{O_2}), decrease in workload, earlier onset of anaerobic threshold, and lower V_{O_2} at the anaerobic threshold. Heart transplant recipients have lower exercise capacity than other transplant recipients.³²⁹ There is evidence to suggest that recipients continue to have abnormalities in both central and peripheral chemoreflex mechanism along with the adverse effects of the immunosuppressive medications that contribute to prolonged deficits of exercise capacity.^{29,64}

Exercise training after transplantation increases exercise capacity, improves endurance, and increases muscle strength, contributing to higher quality of life after transplantation.^{170,233,222,240,329} Physical activity and exercise may reduce or attenuate side effects of immunosuppression. Transplant recipients tolerate progressive exercise training and can achieve near-normal and even normal levels of function.²⁴¹

Various exercises have been prescribed for transplant recipients. Studies have documented various training programs, including aerobic programs of low to high intensities, muscle endurance, and resistive training. It is difficult to make any specific conclusion about the perfect

exercise program. The best recommendation that can be made is to prescribe a comprehensive exercise program that includes muscular strength and endurance training, restoring functional mobility and improving cardiopulmonary endurance.⁹⁸

Research shows that 6 months of specific resistance exercise training (weight training) restores fat-free mass to levels greater than before treatment and dramatically increases skeletal muscle strength. Resistance exercise, as part of a strategy to prevent steroid-induced myopathy, is safe and should be initiated early after transplantation.

Gaining density in the lumbar spine is especially important because up to 35% of transplant recipients develop lumbar spine bone fractures.³⁹ Resistive training has been shown to restore bone density to pretransplant levels compared with an additional 6% loss in subjects who did not participate in resistance training. Marked increase in muscle mass, strength, and exercise capacity was also observed.²⁹¹

Guidelines for Activity and Exercise

Whether assessing aerobic, anaerobic ability, or ADLs (Table 21-4), measurements of vitals, including blood pressure, heart rate, oxygen saturation, respiratory rate, and rate-pressure products (heart rate and systolic blood pressure), can provide valuable information and can be used as measurable outcomes of treatment intervention.

In general, as the intensity of activity increases, the heart rate and systolic blood pressure increase, with a concomitant return to baseline with cessation of activity (see Appendix B). The response the transplant recipient has to exercise will depend on the type of transplant, medications taken, and present level of fitness. For example, heart transplant recipients typically have a blunted heart rate response with exercise due to the denervated state of the heart.

Monitoring the recovery may be an objective measure of improvement in physical capacity. Consistent abnormal responses should be reported to the physician for further evaluation. Other considerations are determined according to the underlying pathologic condition (e.g., cardiomyopathy, congestive heart failure, renal failure, diabetes, cirrhosis) and pretransplant treatment (e.g., VADs, medications, dialysis). See Special Implications for the Therapist boxes for each specific diagnosis in this chapter.

For all transplant candidates and recipients, the duration of beginning aerobic exercise should be until fatigue begins; allow for a short recovery period and repeat in an interval manner until the duration is at least 20 minutes of continuous exercise. The goal is to perform at least 30 minutes of nonstop activity daily at a moderate exertional level before reducing exercise frequency to four to five times weekly. Individuals trying to control blood pressure or lose weight should work for a longer duration, 45 to 60 minutes, at a lower intensity (e.g., 50% to 65% of predicted maximal heart rate).⁹⁸ The exercise program should consider the recipient's comorbidities and be individualized to the needs and goals of the transplant recipient.^{52,166,167}

Table 21-4 Exercise Guidelines for Organ Candidates and Recipients*

- Select an enjoyable activity or exercise and always have a goal! Some centers target a long-term goal by organizing an annual fun run/walk, or join one already organized.
- Include adequate warmup, stretching, and cool-down periods.
- Progress activity or exercise as described in text.
- Include interval training, aerobic activity, strength training, and conditioning.
- Combine activities and/or exercise program with energy conservation techniques (see Box 9-8).
- Maintain a normal breathing pattern; breath holding may contribute to excessive elevation in blood pressure and produce associated symptoms such as dyspnea and lightheadedness.
- Exercise 4 to 5 days a week; allow 24 to 48 hours recovery time after strenuous activity and 48 hours after moderate to vigorous resistance training for those involved muscles.
- Aerobic exercise should be completed 5 days a week for 30 minutes at a moderate intensity level.
- Follow guidelines for neuropathy and myopathy.

Endurance Training: High Repetitions/Low to Moderate Resistance

- Strength training 2 to 3 days a week.
- Use weights that are 50% to 60% of the one repetition maximum.
- Perform 12 to 20 repetitions per set.
- Perform 2 or 3 sets of each exercise per workout.

Weight Training: Low Repetitions/More Resistance

Weight training has become an acceptable component of a comprehensive exercise program. It is recommended to begin strength training at low- to moderate-intensity levels along with a progressive aerobic and stretching program. It is important to assess blood pressure response during exercise and evaluate for signs and symptoms of right-sided heart failure in the presence of pulmonary hypertension. The recipients should also be monitored for hemoptysis, overuse injuries, poorly regulated glucose, electrolyte and nutritional imbalances, and surgical precautions. Anyone with documented pulmonary hypertension may have the following associated signs and symptoms (lightheadedness, dizziness, angina-like pain, decreased cardiac output with exercise, or development of abnormal heart sounds with exertion) needs to be supervised during low-level interval exercises.

Once the person is medically stable and basic level of function is restored, the therapist can more accurately prescribe a supervised exercise program by completing a symptom-limited aerobic exercise test as well as a 1 or 3 repetition maximum. The therapist must take into account any significant impairments present and the effects of long-term steroid use, especially muscle wasting, osteoporosis, and coagulopathy. Risk for injury is higher in this group when using one repetition maximum.

- Determine a one repetition maximum (i.e., the heaviest weight that can be lifted safely at the weakest position in the range of motion one time).
- Use weights that are 40% to 60% of the one repetition maximum.†
- Perform 3 to 8 repetitions per set.
- Perform 3 to 5 sets of each exercise per workout.
- Perform each exercise through a functional range of motion.

For the Therapist

Maintain or Monitor	Terminate Exercise if...
Allow only minimal dyspnea; respiratory rate should be <30 breaths/minute with minimal rales heard on auscultation	Respiratory rate >40 breaths/minute with increased rales
Allow only mild level of fatigue; use rate of perceived exertion (Borg scale; see Table 12-13)	3/10 on Borg scale
Maintain stable vital signs (HR, blood pressure); maintain stable cardiac output (rate/pressure product, pulse pressure)	HR exceeds target zone, decrease in SBP, pulse pressure narrows (SBP – DBP), decrease in rate/pressure product (RPP = HR × SBP)
Maintain stable electrocardiogram	Increased incidence of arrhythmias or perceived palpitations
Maintain central venous pressure (CVP)	Monitor in the presence of right-sided heart failure, maintain CVP >20 mm Hg; terminate exercise relative to other symptoms
Maintain pulmonary arterial pressure (PAP)	Rest is indicated if PAP rises >5 mm Hg; terminate exercise if PAP rises and persists after rest and/or in the presence of other symptoms
Maintain oxygen saturation >90% (this is individually determined by each center according to each person's medical status)	Oxygen saturation <90% (or saturation below prescription)
Monitor for signs of bleeding	See Tables 40-8 and 40-9
Observe client response to exercise; allow moderate level of dyspnea	Change in mental status (e.g., confusion, hostility), onset of pallor or diaphoresis, client request

*Guidelines for exercise are modified for the organ recipient but follow the ACSM's *Guidelines for Exercise Testing and Prescription*. These are only guidelines; each exercise program must be individually tailored to the organ recipient's condition and comorbidities. Progression must be according to tolerance.

†Intensities of 80% to 100% have been shown to produce the most rapid gain in muscle strength within the normal population. However, because of the possibility of overtraining or injury in the pretransplant or posttransplant population, caution must be used when overloading a muscle or muscle group.⁴

HR, Heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Limitations on Activity and Exercise

Transplant trauma is a theoretic possibility, so organ recipients are advised not to participate in contact sports. Except for this general broad precaution, limitations on sporting and exercise must be evaluated on a case-by-case basis and may be determined by the course of the illness. For example, the person who undergoes emergency liver transplantation for acute liver failure will have relatively little secondary damage.

On the other hand, someone with chronic renal failure can develop renal osteodystrophy (see Fig. 18-7 and the section on chronic renal failure in Chapter 18), decreased bone density, osteoporosis, reduced peak cardiac output (because of the arteriovenous fistula required for vascular access), and irreversible neuropathies and myopathies. Anyone experiencing renal failure secondary to diabetes will have multiple other secondary complications (see the section on Diabetes in Chapter 11).

Many other potential limitations on sporting and exercise must be recognized and evaluated, such as the condition of the recipient at the time of transplantation and the type of organ that has failed. For example, people with severe pulmonary disease necessitating heart-lung transplantation often experience malnutrition and muscle wasting before transplantation. Liver failure can cause abnormalities of lung function, including ventilation/perfusion mismatching, pulmonary hypertension, and loss of oxygen-diffusing capacity.

Denervation of the transplanted heart, pancreas, liver, or kidneys results in a loss of sympathetic nerves to the organ (e.g., loss of vagal response in the heart, impaired insulin in the pancreas, and altered renin responses in the kidney) requiring some modifications in the exercise program. In contrast, surgical removal of sympathetic liver nerves does not inhibit hepatic glucose production during exercise, and denervation of the lungs does not impair the ability to increase ventilation during physical exertion.¹⁷⁰

The denervated lung will experience reduced tidal volumes and decreased lung compliance. There is a delay in the bronchodilation response requiring an extended warmup period in order to obtain the catecholamine response necessary for organ vasodilation and therefore increased tidal volume during exercise.

There is evidence that reinnervation does occur to some extent for some recipients. For heart transplant recipients who have some degree of autonomic nervous system function restored, there is an increase in heart rate greater than 35 beats/minute with peak exercise levels and also an immediate decrease in heart rate after exercise. This restoration results in an increase in exercise capacity that is closer to healthy age-matched control subjects.²⁵⁵

Besides the usual exercise-related risks anyone faces, recipients have additional medication-related risks associated with the long-term immunosuppressive therapy, including exaggerated hypertensive response, myopathies, neuropathies, osteoporosis, and fractures.

The adverse effects of the immunosuppressive medications on skeletal muscle, including the muscle-wasting effects of glucocorticoids, are well-known. It is docu-

mented that quadriceps strength of renal transplant candidates is only 70% of normal, although this side effect can be counteracted by resistance exercise training.^{137,138,255} Other potential side effects are listed in Tables 5-3 and 5-4; see also the section on Immunosuppression under Posttransplant Complications in this chapter.

Finally, transplanted organs may be exposed to chronic rejection, limiting the function of the organ. With the decline in organ function there is a decrease in exercise tolerance. For example, in heart transplant recipients chronic rejection is associated with a decrease in cardiac output, onset of heart failure, and accelerated atherosclerosis.³²⁴

With lung transplantation, the recipient suffering from chronic rejection may present with an impairment in gas exchange, leading to desaturation and increased air trapping and work of breathing. However, despite all these variables, the benefits of exercise in maintaining a healthy lifestyle and sense of well-being are much greater than the risks imposed by organ transplantation. Although it is assumed that transplant recipients will spontaneously increase their physical activity after transplantation, fear of harming the new organ or protective family members may discourage vigorous activity.

As a member of the transplantation team, the therapist should encourage a program of regular activity immediately after transplantation and provide exercise guidelines as a part of the long-term transplantation care plan. It is recommended that the recipient be referred for supervised outpatient services since many studies have documented an increase in recovery with supervised exercise as opposed to a home exercise program.²⁹¹

Vigorous exercise training for competition is not contraindicated for healthy transplant recipients. However, cardiorespiratory fitness and strength training should progress gradually before the client engages in more strenuous sports participation. Exercise should be reduced in duration and intensity but not necessarily discontinued during rejection episodes.²⁴⁰

HEMATOPOIETIC CELL TRANSPLANTATION

Definition and Overview

Hematopoietic stem cell transplantation (HSCT) is defined as any transplantation of blood- or marrow-derived hematopoietic stem cells, regardless of transplant type (allogeneic or autologous) or cell source (bone marrow, peripheral blood, or placental or umbilical cord blood).²¹⁹

HSCT, the collection and engraftment of hematopoietic stem cells from the bone marrow (and now also from the peripheral blood and umbilical cord blood) to cure a series of diseases previously considered incurable, is one of the most dramatic developments in the last 30 years.

Initial attempts to transfer techniques derived from animal studies to human beings failed until an understanding of HLA and tissue typing made it possible to select compatible sibling donors and now unrelated

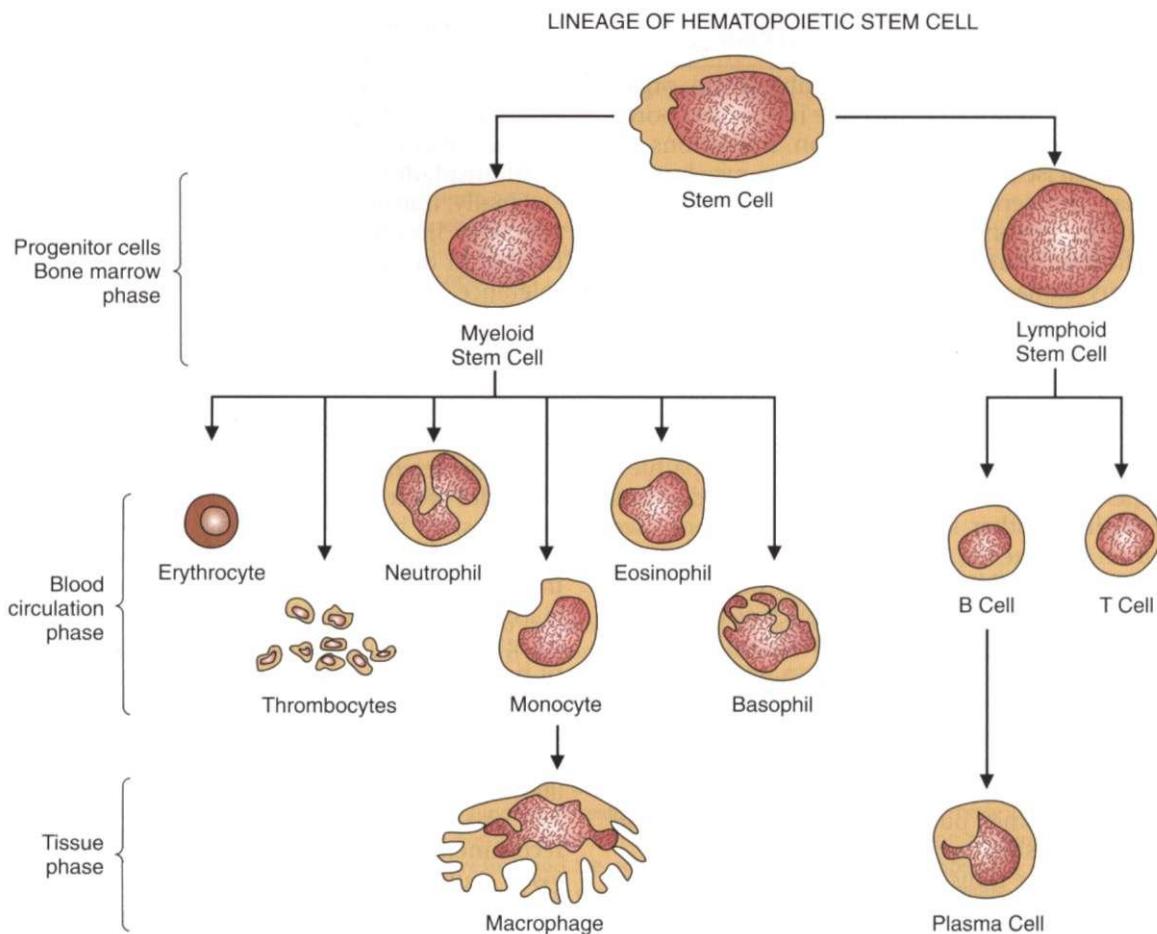


Figure 21-6

A stem cell is any precursor cell or "mother" cell that has the capacity for both replication and differentiation, giving rise to different blood cell lines. This figure shows the origin, development, and structure of thrombocytes, leukocytes, and erythrocytes from pluripotent (able to develop into different cells) stem cells. The process of hematopoiesis (formation and development of blood cells) usually takes place in the bone marrow.

donors. The genes for the HLA, the human major histocompatibility complex, are located on the short arm of chromosome 6; siblings have a 25% chance of being a match.

Nonrelated candidates have less than a 1 in 5000 chance of having identical HLA types. Graft rejection and GVHD rates are inversely related to the degree of HLA compatibility. The National Bone Marrow Donor Registry types people as potential donors for unrelated people who require transplantation.

HSCT is an accepted form of treatment for people who require very high-dose chemotherapy or radiation therapy to treat their disease, usually a type of cancer. The chemotherapy and/or radiation therapy results in severe injury to blood cells formed in the bone marrow (marrow ablation). In order to restore the person's ability to make blood and immune cells, stem cells from a compatible donor (or from the recipient) can be administered.

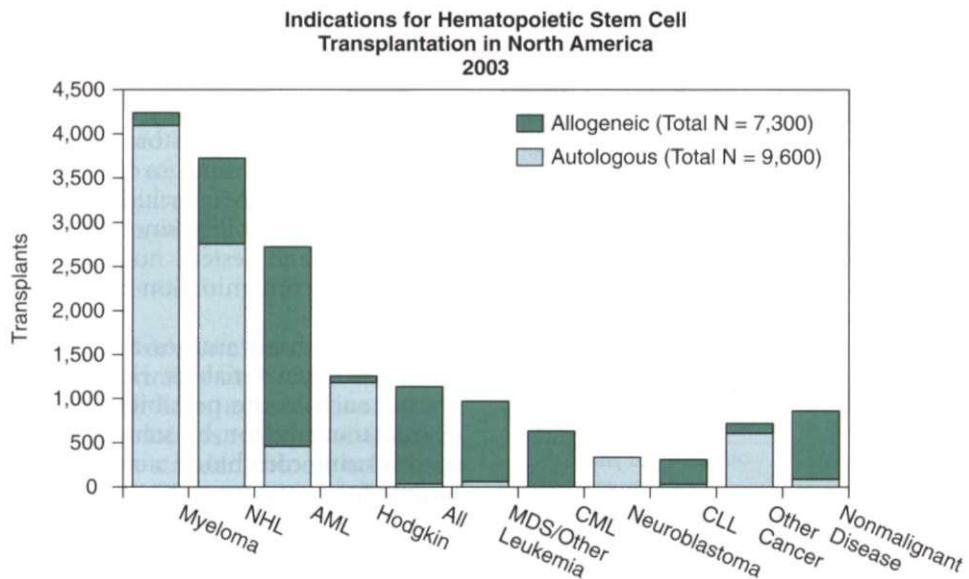
Stem cells are very immature cells that can develop into any of the three types of blood cells (red cells, white cells, platelets) (Fig. 21-6). Bone marrow is used for such transplants because it contains these undifferentiated stem cells. Blood also contains stem cells but in such

small numbers that the cells cannot be counted or identified in ordinary blood tests. New procedures have made it possible to induce stem cells to leave the marrow and enter the blood, where they are collected or harvested for administration to a candidate in need of HSCT. Stem cells are also collected from umbilical cord and placental blood.

Indications for Hematopoietic Cell Transplantation

Today, transplantation of stem cells from peripheral blood, bone marrow, or cord blood is the treatment of choice for a variety of chemotherapy-sensitive hematologic malignancies, solid tumors, syndromes of bone marrow failure, genetic diseases and, more recently, autoimmune disorders. HSCT (peripheral blood stem cell transplantation and BMT) enables individuals to survive high-dose chemotherapy via "rescue" infusion of new, healthy bone marrow elements or stem cells.¹⁰⁹

In 1998 breast cancer was the most common indication for HSCT in North America, accounting for nearly one third of all transplantation procedures. However,

**Figure 21-7**

The most common indications for allogeneic and autologous transplantation differ. *Allogeneic* transplantation is the predominant approach for acute and chronic leukemias; myelodysplasia; and nonmalignant diseases such as aplastic anemia, immune deficiencies, and inherited metabolic disorders. *Autologous* transplantation is used for ovarian and other solid malignancies, as well as Hodgkin and non-Hodgkin lymphomas and multiple myeloma. Routine use of this transplantation for breast cancer has been discontinued and remains under investigation. (Courtesy Center for International Bone & Marrow Transplant Research [CIBMTR]. *CIBMTR Newsletter* 12[1], May 2006.)

subsequent reports have concluded that high-dose chemotherapy plus autologous BMT does not improve survival in women with metastatic breast cancer.^{24,287}

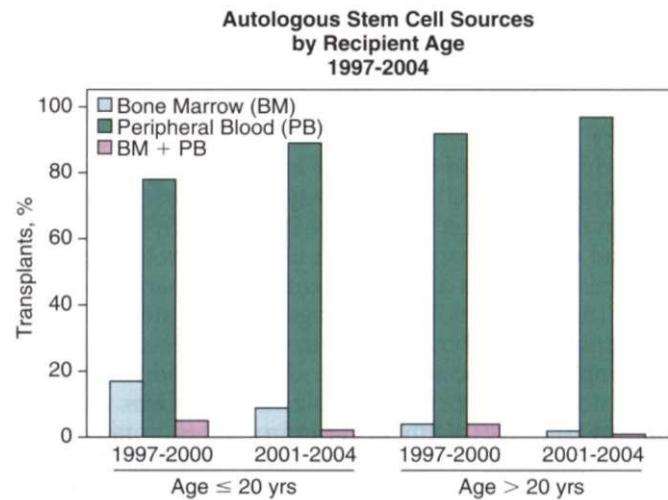
Non-Hodgkin lymphoma was the second most common indication, followed by acute myelogenous leukemia, multiple myeloma, and chronic myelogenous leukemia (Fig. 21-7). Reduced transplant-related mortality rates have led to a widening of indications for HSCT, but based on the experience in the use of stem cell transplantation with metastatic breast cancer, ongoing research is essential to verify the efficacy of this treatment modality for each individual disease entity.²⁰⁸

Sources of Hematopoietic Cell Transplant

The three types of peripheral blood or bone marrow transplantation are determined by the source of the donation: syngeneic, autologous, and allogeneic. The major sources of transplantable hematopoietic stem cells come from human bone marrow, peripheral blood, and umbilical cord blood.³²⁸ As with all other transplants, syngeneic involves peripheral blood or bone marrow from an identical twin with identical HLAs on the cell surfaces.

Autologous transplants use the person's own stem cell sources and must be cancer free by harvesting during remission or after cancer cells have been killed (Fig. 21-8). The person who donates bone marrow for his or her own use does not have cancer in either the bone marrow or the blood cells. This autologous BMT greatly reduces the occurrence of side effects from the transplant.

Allogeneic transplants require a donor with closely matched HLAs (usually a sibling); allogeneic sources for

**Figure 21-8**

Approximately 90% of autologous transplants use only hematopoietic progenitor cells collected from blood. The remainder use bone marrow alone or in combination with cells collected from blood. (Courtesy Center for International Bone & Marrow Transplant Research [CIBMTR]. *CIBMTR Newsletter* 12[1], May 2006.)

stem cell transplantation are primarily derived from bone marrow, with a smaller but steady increase in the number of allogeneic transplants coming from peripheral blood and cord blood (Fig. 21-9). Autologous blood stem cells are now widely used in place of allogeneic BMT, although allogeneic transplantation remains the only curative therapy for inherited disorders of metabolism and chronic myelocytic leukemia and the most effective treatment for severe aplastic anemia.

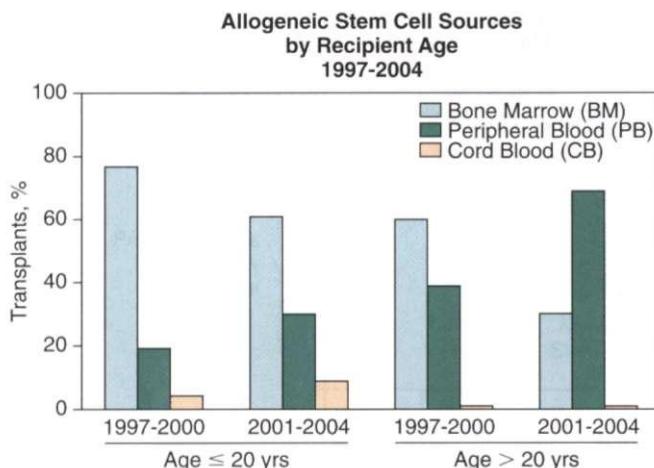


Figure 21-9

Most allogeneic transplants use bone marrow grafts. There has been a steady increase in the number of allogeneic transplants using cells collected from blood. Although use is increasing, there are still relatively few transplants using umbilical cord blood cells. (Courtesy Center for International Bone & Marrow Transplant Research [CIBMTR]. CIBMTR Newsletter 12[1], May 2006.)

Unlike allogeneic transplantation, autologous BMT can be performed in older people with relative safety owing to the freedom from GVHD as a complication. A primary concern with autologous BMT is the possible presence of viable tumor cells in the graft. Numerous methods have been developed to remove contaminating tumor cells from the graft in a process referred to as purging.

Peripheral blood has largely replaced bone marrow as a source of stem cells for autologous recipients. A benefit of harvesting such cells from the donor's peripheral blood instead of bone marrow is that it eliminates the need for general anesthesia associated with bone marrow aspiration. The most striking advantage of blood stem cell over bone marrow cell transplants is the shortened period of total aplasia of bone marrow after chemotherapy. This reduction in the period of aplasia may allow repeated marrow ablative treatment cycles in solid tumors, thereby reducing mortality. In addition, blood-derived grafts may contain fewer malignant cells than the bone marrow cells.

Since the late 1980s umbilical cord blood has been harvested to assist people in need of stem cells previously only available through BMTs. Umbilical cord blood is the blood that remains in the umbilical cord and placenta after a baby is born. It is derived from the portion of the umbilical cord that has been cut and is usually thrown away. Like bone marrow, cord blood has been found to be a rich source of stem cells and may provide treatment advantages over bone marrow, especially if it comes from an immediate family member.

Family members wishing to store their newborn's cord blood for their own potential use can do so for a fee. However, anyone with a family member who has a condition for which stem cells may be a treatment option can store cord blood at no cost through the Cord Blood Registry's Designated Transplant Program. Contact the

Cord Blood Registry at (888) 267-3256, (888) 932-6568, or www.cordblood.com to learn more about banking cord blood. Cord blood banking is the process of collecting the blood immediately after delivery and freezing it for long-term cryogenic storage.

The potential advantages of cord blood stem cell transplantation over BMT include a large potential donor pool, rapid availability since the cord blood has been prescreened and tested, no risk or discomfort to the donor, rare contamination by viruses, and lower risk of GVHD.

Potential disadvantages are primarily related to the many unknown variables with a new, experimental procedure, such as the possibility of genetic or congenital disease transmission by stem cells, uncertain long-term success using cord blood stem cells, and a longer period of time for treatment to be effective compared with cells from adult blood or bone marrow, leaving the recipient at risk for infection. It remains unknown how long cord blood can be stored without losing its effectiveness.

Transplantation Procedure

HSCT involves the intravenous infusion of hematopoietic progenitor cells from the patient (autologous) or an HLA-matched donor (allogeneic). Before transplantation, the recipient undergoes a conditioning regimen with high-dose chemotherapy or radiotherapy (or both) to destroy defective bone marrow or residual cancer cells.²⁶⁸

Allogeneic transplant recipients remain hospitalized until their absolute neutrophil count exceeds $1500/\text{mm}^3$ for 48 hours (normal values are 3000 to $7000/\text{mm}^3$). Autologous transplant recipients may be managed as outpatients. All transplanted individuals are expected to remain geographically near during the first 100 days after transplantation, when the incidence of acute rejection is the greatest, and to use reverse isolation (mask and glove wear) until they reach an acceptable neutrophil level.¹⁰⁹

Bone Marrow

The BMT process consists of several phases: conditioning, harvest, marrow infusion, preengraftment, and engraftment. Conditioning refers to the immunosuppression treatment regimen of chemotherapy, radiation therapy, or both used to eradicate all malignant cells, provide a state of immunosuppression, and create space in the bone marrow for the engraftment of the new marrow. Conditioning occurs 7 to 10 days before the actual BMT takes place.

Bone marrow is withdrawn from the donor by needle aspiration from the iliac crest or sternum on an outpatient basis and does not require surgical intervention. The donated marrow is usually infused through an intravenous line 48 to 72 hours after the last dose of chemotherapy or radiation therapy.

Peripheral Blood Stem Cells

Peripheral blood stem cells are harvested from the person's own stem cells through a process referred to as *leukapheresis*. Leukapheresis, or hemapheresis, is the process of removing a donor's blood to extract a specific component and returning the unneeded parts to the donor. The

process uses continuous circulation of blood from a donor through an apparatus and back to the donor, making it possible to remove desired elements from large volumes of blood. Besides stem cells, this process can separately harvest platelets, red blood cells, white blood cells, or plasma. The infused cells usually begin producing new blood cells in the marrow within a few weeks, and immune function returns within 1 to 2 years in successful transplants.

Cord Blood

Collection of cord blood takes place immediately after the umbilical cord is clamped after birth. After the baby is removed from the delivery area, a needle is inserted into the umbilical vein and blood is withdrawn and collected by gravity drainage. A standard blood collection bag is used, containing nutrients and an anticoagulant solution to keep blood from clotting.

An alternate method involves collecting the cord blood after the child is delivered but before the placenta is delivered. This collection method may be advantageous because it allows earlier collection before the blood has a chance to clot, and it uses the contractions of the uterus to enhance blood collection. This second technique is more intrusive and may potentially interfere with the mother's care after delivery.

After collection, the bag of cord blood is immediately transported to a facility for testing (e.g., HLA typing, identification of any viruses) and preservation. The blood is then frozen and held in liquid nitrogen at very low temperatures for future use. At the time of transplantation, the cord blood is thawed and infused through a vein into the recipient.

Umbilical cord blood stem cells are different than other types of stem cells. Umbilical cord blood stem cells are the "youngest" safely available stem cells and the product of a live birth. Freezing these cells essentially stops the clock and prevents aging and damage that may occur to the cells later in life.

Another source of stem cells, embryonic stem cells, has been at the heart of heated debate.¹⁸⁶ Currently, embryonic stem cells are not being used to treat human beings. A third category of stem cells is adult stem cells, such as those found in bone marrow as previously discussed. Adult stem cells serve very specialized roles in children and adults and are not as proliferative as those found in cord blood.

Complications of Hematopoietic Cell Transplantation

Many people entering transplantation have already developed significant multisystem depletion, including cardio-pulmonary, nutritional, musculoskeletal, and neurologic impairment related to the underlying disease. Bone metastasis, steroid myopathy, polyneuropathies, depleted protein stores, and impaired skin integrity are common comorbidities before HSCT transplantation (Box 21-8).

The high-dose chemotherapy and radiation typically used as the preparative regimen for HSCT produces considerable morbidity and mortality. Virtually all HSCT recipients rapidly lose all T and B lymphocytes after con-

Box 21-8

COMPLICATIONS ASSOCIATED WITH HEMATOPOIETIC TRANSPLANTATION

Pretransplantation

- Effects of immune suppression (see Table 5-3)
 - Steroid myopathies, neuropathies
 - Immobility
 - Weakness
 - Renal failure
- Effects of chemotherapy and radiation therapy (see Tables 5-7 and 5-8)
 - Cognitive impairment
 - Neurologic impairment
 - Neutropenia
 - Thrombocytopenia
 - Hemorrhage
 - Anemia
 - Cardiopulmonary toxicity
 - Arrhythmias
 - Cardiomyopathy
 - Interstitial pneumonitis
 - Obstructive or restrictive disease
 - Nutritional deficits
 - Bone metastasis
 - Impaired skin integrity

Posttransplantation

- Infection
- GVHD (see Box 21-6)
- Recurrence of malignancy
- Sterility
- Cystitis
- Veno-occlusive liver disease
- Fatigue
- Hearing loss (ototoxic antibiotics)
- Delayed effects of radiation
 - Visual loss (cataract formation)

ditioning, losing immune memory accumulated through lifetime exposure to infectious agents, environmental antigens, and vaccines.

Transfer of donor immunity to HSCT recipients is variable and cannot be relied on to provide long-term immunity against infectious diseases. Cognitive slowing, impaired memory, and impaired executive functions are also seen in people following interferon-alpha treatments and whole-brain irradiation.³²³

Neurologic complications occur in accordance with the stage of HSCT. For example, during conditioning, drug-related encephalopathies and seizures or complications secondary to medical procedures are possible. During bone marrow depletion, metabolic and drug-related encephalopathies and seizures, septic cerebral infarctions, and hemorrhages may occur. Chronic immunosuppression results in infections by viruses and opportunistic organisms, and late events such as central nervous system relapses of the original disease, neurologic complications of graft versus host disease, and second neoplasms are observed. The frequency and type of neurologic complication depends on the type of HSCT and the underlying disease.²⁶⁸

Cardiac or pulmonary toxicity also may occur as a result of the irradiation and immunosuppressive drugs used to prepare candidates for the transplantation. Interstitial pneumonitis, an inflammation of the lungs, is a common complication, especially among allogeneic transplantations, which leaves the person susceptible to obstructive small airway disease. Arrhythmias may be the first sign that a chemotherapeutic agent is becoming cardiotoxic.

Infections and hemorrhagic complications during the period of bone marrow anaplasia and emerging immune competence and GVHD are the most life-threatening complications of BMT, and they may be fatal. Rejection of allogeneic transplantation resulting in infection, relapse, or GVHD is often fatal. Infections include early bacterial infections or later opportunistic infections, especially CMV interstitial lung disease. EBV-associated lymphoproliferative disorders (posttransplantation lymphoproliferative disorders) are a significant problem after stem cell transplantation from unrelated donors or mismatched family members.¹³⁰

Recurrence of malignancy is always a possibility. Other complications of BMT include sterility, cystitis, cataract formation, cardiomyopathy, and veno-occlusive liver disease. Neuromuscular changes, such as peripheral neuropathies, muscle cramping, and steroid myopathies, may also develop.

The complications of PBSCT are essentially the same as those of BMT, but hematologic recovery after PBSCT is much more rapid (10 to 12 days and as early as 7 days), thereby significantly shortening the period of postchemotherapy neutropenia (decreased neutrophils, a type of granular leukocyte used to fight infection) and thrombocytopenia (decreased platelets in peripheral blood). This, in turn, reduces platelet and red blood cell transfusion and facilitates earlier discharge from the hospital. In most cases, PBSCT can be performed on an outpatient basis.

Prognosis

Enormous progress has been made in understanding the biology, therapy, and prophylaxis strategies of transplantation and in extending the range of potential bone marrow donors to include unrelated people. Dramatic advances have occurred in the prevention of serious infection, including CMV infection, formerly a significant cause of mortality.

One-hundred-day mortality, defined as death before 100 days after transplant, is often used as a gauge of procedure-related toxicity. Allogeneic transplants are associated with relatively high risks of GVHD, failure of engraftment, infections, and liver toxicity, resulting in high early mortality. Long-term survival rates are improved with BMT, but this type of transplantation does not confer a normal life span.^{285,305}

Unfortunately, toxicities of conventional transplantation remain a major limitation to successful application of the procedure. Primary disease recurrence continues to account for the majority of deaths in autologous transplant recipients. New cancer, organ failure, and suicide are also cited as causes of death among long-term survi-

vors after BMT. The incidence of suicide is higher among such survivors than among healthy subjects.²¹⁶

Despite high morbidity and mortality after HSCT, recipients who survive long term are likely to enjoy good health. For those who survive more than 5 years after HSCT, 93% are in good health and 89% return to work or school full time. Eighty-eight percent of those who survive 10 years after HSCT report that the benefits of transplantation outweigh the side effects.²⁸⁹

Although the success rates of transplantation have been improving over time, the prognosis still depends on the underlying disease, delays in transplantation, associated risk of relapse (e.g., leukemia) and current remission state, the development of GVHD based on the level of match between donor and recipient, and the age of the recipient. There is no effective therapy for severe GVHD, and people stricken with it rarely recover.

The success of allogeneic marrow grafting is inversely proportional to the age of the recipient. Most marrow transplant centers do not perform transplantations in anyone older than 50 years, but some groups do make treatment decisions on the basis of a person's estimated physiologic age rather than chronologic age. These age restrictions do not apply to syngeneic or autologous transplants because these people will not develop GVHD. However, people older than 60 years do not tolerate intensive treatment as well as younger people.

Future Trends

The development of techniques to achieve a state of chimerism and continued research efforts toward improved tolerance and elimination of malignant cells will lead to a wider application of HSCT in the coming decade.³⁰⁴ Infusing donor bone marrow as an adjunct to solid-organ transplantation in order to prevent organ rejection is being investigated with animal studies.²⁴⁹ This would open up an entirely new application of BMT and potentially alter the need for exogenous immunosuppression.

Efforts to reduce acute and long-term side effects of the high-dose conditioning regimens currently required to control the malignancy and prevent graft rejection may extend the use of allografts for people older than 55 years or for younger people with certain preexisting organ damage.⁵⁶ Transplantation using less toxic preparations may also make it possible to treat autoimmune diseases in the years ahead.

Researchers have located a master (stem) cell in the bone marrow of rats that will convert itself into functioning liver tissue cells under special conditions.²⁴⁸ Preliminary studies from the same laboratory have also isolated a stem cell that converts into pancreatic cells. Other laboratory research has found in bone marrow the stem cells for bone, cartilage, tendon, muscle, and fat.^{150,253} Although this work has been only demonstrated in laboratory animals, it is a significant step toward learning how to regenerate human organs.

Swedish scientists isolated and identified for the first time the neural stem cell responsible for forming adult brain cells. This finding supports the idea that brain and other neural tissues regenerate despite conventional belief that these tissues do not regenerate.^{154,155,217} Manipulation

of these cells could open the door for replacing damaged neural tissues in spinal cord injuries and other neurologic conditions, such as multiple sclerosis, Huntington chorea, and Parkinson's disease.

SPECIAL IMPLICATIONS FOR THE THERAPIST 21-1

Hematopoietic Stem Cell Transplantation

PREFERRED PRACTICE PATTERNS

4A, 4B, 4C, 4G: One or more musculoskeletal patterns may be present depending on the complications present (e.g., bone metastasis, steroid myopathy, cancer-related surgery) (see previous discussion of complications associated with blood and bone marrow transplantation; see also Box 21-8)

5G: Impaired Motor Function and Sensory Integrity Associated with Acute or Chronic Polyneuropathies

6B: Impaired Aerobic Capacity/Endurance Associated with Deconditioning

6C: Impaired Ventilation, Respiration/Gas Exchange, and Aerobic Capacity/Endurance Associated with Airway Clearance Dysfunction

7A: Primary Prevention/Risk Reduction for Integumentary Disorders

7B: Impaired Integumentary Associated with Superficial Skin Involvement

The therapist's evaluation must include past medical history to assess other medical conditions, relevant past surgery, and prior level of exercise. Assessment of strength, skin condition, presence of neuropathy and myopathy, and balance impairment is necessary as part of the total evaluation with these individuals because of the specific medical treatment regimen associated with this type of transplantation.

The combination of these factors puts the person at risk for immobility and subsequent pneumonia, pressure ulcers, muscle weakness, and overall deconditioning. In addition, long-term side effects of chemotherapy include peripheral neuropathy, and the prolonged use of steroids can induce steroid myopathy and osteoporosis. Any of these conditions places the individual at risk for falls and associated injuries.

Skin inspection and skin care are of primary importance to prevent pressure or shear injuries. The therapist must evaluate the need for turning schedules, specialized mattress surfaces, and wheelchair cushions. The client must be instructed in self-inspection, especially when splinting is used to treat neuropathic weakness and proprioceptive loss.

Exercise After Hematopoietic Stem Cell Transplantation

Although initiating exercise after peripheral blood stem cell transplantation has been delayed up to 30 days, there is evidence that aerobic exercise can be safely carried out immediately after HSCT and can partially prevent loss of physical performance⁸⁰ depending on the medical and physical condition both before the transplant and after transplant and

chemotherapy. See the section on Exercise, Activity, Sports, and Organ Transplantation in this chapter. Exercise following BMT may be delayed longer owing to the intensity of the course of treatment required.

Exercise capacity in BMT recipients is low when transplantation is preceded by cardiotoxic chemotherapy or irradiation. Reduced exercise endurance, reduced maximal oxygen consumption, reduced rise in cardiac output during exercise, and reduced ventilatory anaerobic threshold are closely related to the chemotherapy.¹⁴⁹

Extremely abnormal responses require consultation with the physician before therapy is initiated or continued. These clients may need continuous monitoring over many therapy sessions rather than just using symptoms as a guide to exercise tolerance once a baseline is established.

Training studies of candidates before BMT to evaluate the impact of inactivity have not been performed. However, it has been demonstrated in individuals who have undergone BMT that a treadmill walking program started 18 to 42 days after transplantation results in significant improvement in maximal physical performance, walking distance, and lowered heart rate at a given workload.⁸³ Active exercise, muscle stretching, and treadmill walking have been shown to increase muscle strength after allogeneic BMT.²¹²

Aerobic exercise improves the physical performance of peripheral stem cell recipients who have undergone high-dose chemotherapy. To reduce fatigue, this group of individuals should be counseled to increase physical activity rather than rest after treatment.⁷⁹

During transplant induction and in the acute post-transplant phase, recipients must be encouraged to remain mobile and maintain ADLs despite the many unpleasant symptoms present. The loss of white blood cells exposes the individual to infection, while the depletion of red blood cells reduces energy, resulting in profound fatigue. Pulmonary conditioning with inspiratory muscle training, muscular strengthening, and endurance exercises is important to help maintain mobility but must be balanced with pacing, prioritizing, and other energy conservation techniques as an important part of treatment.

Range of motion, supervised or assisted ambulation, and resistive or endurance exercises can be utilized. Active assisted and passive range of motion is sometimes required for joint disuse and stiffness. Resistive exercises in the form of functional activities such as bridging, transfers, and walking are individually prescribed.¹⁰⁹

Interval activity training (see Appendix B) combined with energy conservation techniques (see Box 9-8) is an important component of therapy since the client's blood counts drop (including hemoglobin count, resulting in anemia), thereby reducing the body's capacity for exertion or aerobic activity.

Decreased platelet counts increase the person's susceptibility to bleeding from minor injuries. The amount of resistance and the use of equipment to

Continued.

provide resistance depend on platelet count. The therapist must monitor blood values to avoid causing joint hemorrhage (see Tables 40-8 and 40-9). Safety education is important, and assistive devices may be needed.

Infection

Myelosuppression as a result of specific chemotherapeutic agents or drug combinations is the number one factor that predisposes the person to infection (see Box 8-1). Until bone marrow function returns, the HSCT recipient is extremely susceptible to life-threatening infection, which requires all staff to practice interventions to minimize or prevent infection, such as good handwashing technique.

Preventing infections among HSCT recipients is preferable to treating infections. Any therapist working with this population is advised to obtain the guidelines for preventing opportunistic infections among HSCT recipients available from the Centers for Disease Control and Prevention.²¹⁹ See also Chapter 8.

Therapists and nursing staff must work closely together to prevent infection, recognize early signs of infection or rejection, and reinforce the educational program, which is complex and is often taught in a short time under less than ideal conditions. Expanding the lungs regularly during common movements, such as when getting out of bed or turning, while coughing, and during exercise, is an important part of minimizing infections.

Graft-Versus-Host Disease

Early symptoms of GVHD (see previous discussion in this chapter) usually appear within 10 to 30 days after transplantation and may include rash, hepatomegaly, and diarrhea. Although some cardiopulmonary abnormalities can only be detected by echocardiography, early warning symptoms of cardiopulmonary complications, such as progressive dyspnea, sensation of heart palpitations, irregular heartbeats, chest pain or discomfort, or increasing fatigue, may be reported by the recipient or observed by the therapist. The physician must be notified of such changes and modifications made to the exercise program for mildly to moderately abnormal responses.

Monitoring Vital Signs

Vital signs must be monitored before, during, and after exercise to assess each HSCT recipient for an abnormal response. At this time, no data show the effects of drug interventions or the physiologic responses to transplant procedures in recovery or over the long term. Monitoring responses over time during the recovery process can alert the therapist to any developing cardiopulmonary compromise.

The concept of routine monitoring applies to anyone who is seemingly healthy after transplant and may provide helpful information about when to advance an exercise program. Knowledge of past medical history and preexisting conditions that could affect physical conditioning is essential. Preexisting conditions in the presence of extended periods of

inactivity can contribute to further physical deconditioning.

Normal changes in vital signs include an increased heart rate and increased systolic blood pressure proportional to the workload, with minimal change in diastolic blood pressure (no more than ± 10 mm Hg). Hypertension or the use of antihypertensive medications (or other medications) can alter the normal response of blood pressure to exercise. Recipients may be deconditioned with a less than normal (sluggish) blood pressure response (see Appendix B).

Monitoring Laboratory Values

In addition to monitoring vital signs, the therapist must be aware of daily laboratory values for red blood cells, white blood cells, and platelets. Each facility will have its own guidelines for activity and exercise based on blood counts. Often, symptomatology is used as the primary measure of acceptable activity. Platelet levels must be evaluated (thrombocytopenia) before chest percussion is performed. See also the sections on Radiation Injuries and Chemotherapy in Chapter 5.

ORGAN TRANSPLANTATION

Kidney Transplantation

Overview

The first kidney transplantation was done in 1954 by Joseph Murray, MD, resulting in a successful graft and providing the recipient with an additional 8 years of life. It was the first organ transplantation of any kind ever performed, with the success credited to the live donor (adult twin brother). Kidney transplantation remains the most common type of solid-organ transplant (see Table 21-1).

As people over the age of 65 years become the fastest growing segment of the population, the number of cases of end-stage renal disease (ESRD) requiring kidney transplantation will continue to increase. Diabetes is now the most common cause of ESRD. Almost half of adults undergoing transplantation already have diabetes.

Renal replacement remains the most successful form of treatment for ESRD and, in the case of diabetes, offers an opportunity to eliminate dependence on dialysis and exogenous insulin. Simultaneous kidney-pancreas transplantation has become a safe and effective method to treat advanced diabetic nephropathy and results in stable metabolic function, reduced cholesterol, and improved blood pressure control.²⁹⁷

Until recently, almost all candidates for renal transplantation had been treated for months or years with hemodialysis, but now it is possible to plan a kidney transplant before the complete shutdown of the kidney or kidneys, avoiding dialysis completely. Studies have shown that when dialysis is used, peritoneal dialysis is associated with a lower incidence of delayed graft function and may be preferred over hemodialysis.^{29,327}

Continuous ambulatory peritoneal dialysis is a maintenance system of dialysis in which an indwelling catheter permits fluid to drain into and out of the peritoneal cavity by gravity. The individual remains able to complete this type of dialysis three or four times per day while at home rather than coming to a hemodialysis clinic three or four times per week for 3 or 4 hours at a time while the blood is filtered through a dialysis machine.

Receiving a kidney transplant without a prior history of hemodialysis or peritoneal dialysis presents some problems in adjustment for those people who, never having experienced the intrusion of dialysis, must now learn to live with the side effects of antirejection drugs and potential complications of surgery. Whereas the person on dialysis may see transplantation as a welcome relief, recipients who have never been treated with dialysis may be more likely to view the surgery and recovery as an ordeal and therefore experience more difficulties in adjustment.

Indications and Incidence

The primary indication for renal transplantation is type 1 diabetes with ESRD, which occurs in over one third of all cases of type 1 diabetes.¹⁹⁷ Cardiac autonomic neuropathy occurs as a result of uremia and diabetes with severe cardiac dysfunction when these conditions occur at the same time. Both kidney transplantation and kidney-pancreas transplantation result in improved cardiac autonomic function and modulation of heart rate.¹⁹⁸

There are now more than 50,000 people on the waiting list for cadaveric kidney transplant, but only 14,000 of these procedures are performed yearly in the United States.¹²¹ A more unusual indication would be polycystic kidney disease, especially when combined with polycystic liver disease.

Transplant Candidates

As mentioned, people with type 1 diabetes and ESRD can choose dialysis or transplantation for renal replacement therapy. Those individuals with type 1 diabetes younger than 45 years with little or no atherosclerotic vascular disease are ideal candidates for a combined kidney-pancreas transplantation. The addition of a pancreas transplant is associated with greater morbidity and may require higher levels of immunosuppression but can result in stabilization of neuropathy and improved quality of life.¹⁹⁷

Some renal transplant candidates are at high risk for cardiac events, sometimes fatal. Analysis of these clinical risk factors (including age at least 50 years, type 1 diabetes mellitus, and abnormal electrocardiogram) may assist in identifying candidates who may be at risk for cardiac death.¹⁸⁸ For those choosing transplantation, a kidney from a living related donor is associated with longer graft and individual survival.

Transplantation Procedure

Kidney grafts may be positioned intraperitoneally, anastomosed to the iliac vessels, and then drained into the bladder (Fig. 21-10); extraperitoneally in the iliac fossa through an oblique lower abdominal incision; or in small

children, retroperitoneally with a midline abdominal incision.

More recently a procedure called laparoscopic nephrectomy has been introduced to remove the live-donor kidney. Four small incisions called ports are made in the abdomen. The ports allow the surgeon to insert the laparoscope and other instruments used in the procedure to clamp off arteries and the ureter and cut the kidney loose.

Complications

As with other solid-organ transplantation, renal recipients experience graft dysfunction, organ-related infection (nephrotoxicity), and graft rejection as the three most common complications. Surgical complications include renal artery thrombosis, urinary leak, and lymphocele, although chronic rejection accounts for most renal allograft losses after the first year after transplantation. Donor organ quality, delayed graft function, and other donor and recipient variables leading to reduced nephron mass are nonimmunologic factors that contribute to the progressive deterioration of renal graft function.²¹⁸

Cardiovascular and cerebrovascular diseases are major causes of morbidity and mortality after kidney transplantation. Extensive carotid vascular wall abnormalities increase significantly despite kidney and pancreas transplantation in those individuals with type 1 diabetes mellitus and progressive uremia.

Although initiation of plaque development is related to systemic factors, progression of established plaque is largely influenced by local factors within the arterial wall and therefore unaffected by organ transplantation.²²³ In fact, research has shown an association between CMV infection and atherosclerotic plaque formation in coronary heart disease, a finding that has also been found in posttransplant cardiac complications in kidney recipients with CMV.¹⁴²

Other complications may include renal dysfunction with prolonged use of cyclosporine, hypertension, lipid disorders, hepatitis, cancer, and osteopenia. Hypertension occurs in up to 80% of renal graft recipients; approximately 15% of graft recipients develop chronic hepatitis. There is a high degree of impaired bone formation associated with renal grafts, resulting in severe osteoporosis when compared with other organ transplants.

Basal cell and squamous cell carcinoma, Kaposi sarcoma, lymphomas, and posttransplant lymphoproliferative disease are 20 times more frequent in this population. Kidney cancer is 15 times more common after kidney transplantation compare with the general population. Melanoma, leukemia, hepatobiliary tumors, and cervical and vulvovaginal tumors are five times more likely compared with the general population. Testicular and bladder cancers are three times more common.¹⁶¹

Pelvic congestion syndrome can occur in a kidney donor or recipient when removal of the kidney ligates the ovarian vein. Retrograde flow in the ovarian vein causing ovarian varicosities (varicose veins of the ovaries) with venous stasis produces congestion and chronic pelvic pain in some women.²⁰ Imaging studies have verified the fact that there are very few venous valves in the blood vessels of the pelvic area.^{91,133,300} Any compromise of the

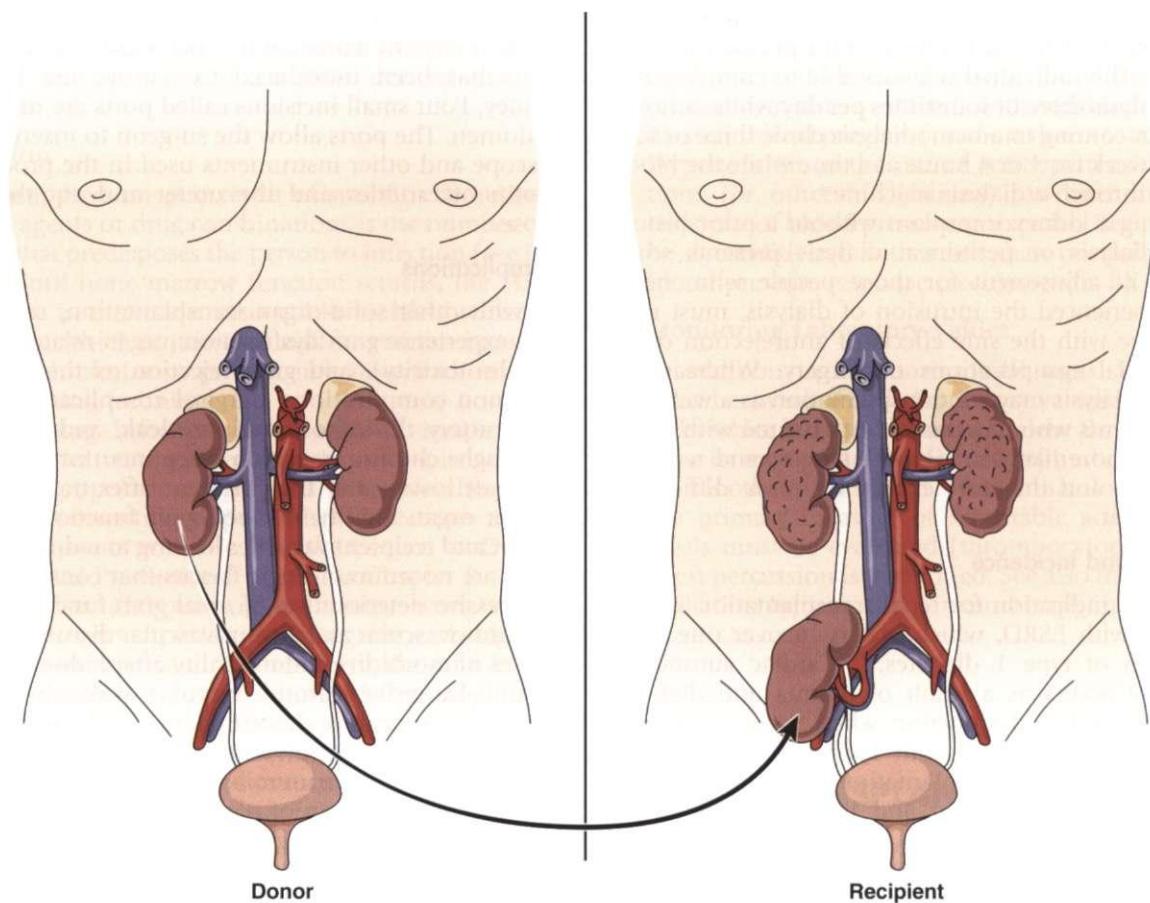


Figure 21-10

In a minimally invasive live-donor kidney transplantation, surgeons remove the donor's kidney through a 3- to 4-inch incision below the donor's umbilicus. For the recipient, blood vessels of the donor kidney are attached to the major abdominal blood vessels. The ureter of the donor kidney is attached to the recipient's bladder. The donor kidney begins working immediately. The recipient's own malfunctioning kidney is not always removed.

valves or blood vessels in the area can result in pelvic congestion syndrome.

Prognosis

Long-term renal transplant survival has improved from 23% (graft) and 36% (recipient) for cadaveric donor in 1986 to 92% and 93%, respectively, in 1996.³²¹ The long-term outcome of simultaneous kidney-pancreas transplant recipients is not well established yet and ranges from 79% for a 1-year graft survival rate to 5-year survival rates for combined kidney-pancreas transplant, kidney transplant, and pancreas transplant reported as 95%, 85%, and 88%, respectively.²⁹⁷

Future Trends

The renal research community has made great strides in improving client outcomes on dialysis and following organ transplantation. However, only a small fraction of individuals with ESRD undergo transplantation because of a lack of donor organs, requiring continued research to find alternative methods of successful treatment. Alternately, preserving donor organs more effectively may ensure better graft survival rates. Since both glomerular

and tubular functions are inhibited at temperatures below 18° C, efforts to develop organ preservation techniques at warmer temperatures are underway.²⁹⁴

Current research continues to examine the possibilities of reducing cyclosporine dosage through the concomitant use of sirolimus without increased infections or neoplasms developing and with the potential for reducing the incidence or progression of chronic rejection. Other efforts to reduce the incidence of acute rejection episodes include assessment of a chimeric monoclonal antibody.¹⁵⁸

The search for adult renal stem cells for cell-based treatment is ongoing.⁴⁰ At the same time, a bioartificial (extracorporeal) kidney has been successfully engineered. The unit includes a conventional dialysis filter (cartridge that filters the blood) connected to a renal tubule assist device that contains human tubule cells, which reclaim electrolytes, salt, glucose, and water lost in traditional dialysis. This therapeutic modality may decrease the survival gap between current renal replacement therapies and healthy kidney functions.³⁰⁸

Acute renal failure has a high mortality rate despite hemodialysis or continuous renal replacement therapy.

The first human trial of a bioartificial kidney was reported in October 2004.¹⁴⁵ The hope is that complications of acute renal failure due to excessive inflammation can be delayed or avoided while giving the patient's own kidney time to recover. Six of the 10 patients who received the unit who were expected to die recovered. Phase I and II clinical trials show that such a device replaces multiple kidney function and improves survival in acute renal failure.³⁰⁷

SPECIAL IMPLICATIONS FOR THE THERAPIST 21-2

Kidney Transplantation

PREFERRED PRACTICE PATTERNS

4A: Primary Prevention/Risk Reduction for Skeletal Demobilization

4B: Impaired Posture

4D: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Connective Tissue Dysfunction (ligament or tendon disorder)

5G: Impaired Motor Function and Sensory Integrity Associated with Polyneuropathies

6B: Impaired Aerobic Capacity/Endurance Associated with Deconditioning

6C: Impaired Ventilation, Respiration/Gas Exchange, and Aerobic Capacity/Endurance Associated with Airway Clearance Dysfunction

7A: Primary Prevention/Risk Reduction for Integumentary Disorders

As an increasing number of studies document the effectiveness of exercise in disease prevention and prevention of transplant complications, timely and effective rehabilitation programs will be implemented. Physical and occupational therapy can offer a great deal to renal rehabilitation, especially to increase endurance and physical strength and to improve function and independence (see the section on Exercise, Activity, Sports, and Organ Transplantation in this chapter).

Given the high rate of malignancies in this population, the therapist should continue to work with the recipients in cancer education and prevention. Cancer screening is an important ongoing feature of any physical therapy examination and evaluation with this population.

Acute Care Phase

Most kidney recipients are discharged about 5 days after surgery and are not seen by the therapist until later in the recovery process (or perhaps not at all) as an outpatient approximately 1 month postoperatively. At that time, the recipient will most likely still monitor both blood pressure and blood glucose levels. The therapist should pay close attention to both these measurements as the rehabilitation component is added.

Exercise

Kidney transplants have been performed longer than any other organ, providing a greater number of retro-

spective studies to assess the influence of exercise on kidney transplantation. It has been shown that pretransplant and posttransplant exercise training improves lipid profile, increases hematocrit level, normalizes insulin sensitivity, and lowers the requirement for antihypertensive medication.^{111,112}

Although a kidney transplant recipient may be normotensive at rest, there is an elevated blood pressure response to exercise, possibly caused by altered function of blood pressure control and by the effects of cyclosporine. This requires careful monitoring and documentation of vital signs in the exercise program planning and assessment.

Training effectively modifies factors known to be associated with atherogenesis and cardiac disease in hemodialysis clients. However, exercise training alone after renal transplantation is not enough to modify cardiovascular risk profile. Research to determine the effects of multiple risk interventions is needed.¹⁴²

Before transplantation, clients with kidney disease, especially those receiving hemodialysis, are susceptible to bone loss as a result of altered vitamin D₃ function and its role in calcium absorption. Resistive exercises can help increase bone density (in the general population and in all organ transplantations) and should be initiated before transplantation or as early after transplantation as possible.^{38,182,220}

Overuse tendon injuries occur at a high rate in kidney transplant recipients^{3,221}; whether the mechanism for this is immunologic, metabolic, or medication induced remains unclear. The use of fluoroquinolones (potent oral antibiotics such as levofloxacin, ciprofloxacin, norfloxacin) has been linked as a responsible factor.^{200,211,339} The Achilles is the most commonly reported tendon injury, but injury can occur in the upper extremities as well. For anyone taking fluoroquinolones, care should be taken to avoid overloading tendons since dramatic ruptures following even small trauma have been reported.²⁸²

Bladder Transplantation

Research is underway to engineer bladder tissue substitutes. Tissue grown from the person's own cells has been used to engineer bladder regeneration in young children. This is a tissue engineering feat more than actual organ transplantation. A number of synthetic and natural materials have been used in experimental settings. The production of functional bladder tissue replacements has not been completed yet.¹⁷⁷

Damaged bladder tissue was removed in a small number of children aged 4 to 19 years with bladder impairment associated with myelomeningocele. Normal, healthy bladder (urothelial and muscle) cells were harvested and reproduced in a laboratory setting, then reintroduced into the remaining bladder. Since autogeneic tissue was used, there were no side effects from the grafting procedure and no rejection.¹⁶

Liver Transplantation

Overview

The first liver transplant in a human being was performed in 1963. Since that time, the success of this procedure has improved so much that 1600 liver transplants were completed in the United States in 1990. In the following decade, a team of surgeons at the University of Chicago developed the living related transplant that requires only a lobe of a liver or small pieces taken from living donors. This technique has also been applied to cadaveric donor livers by splitting the liver to expand the donor pool.⁴⁴

Indications

Orthotopic liver transplantation has become an established therapy for end-stage liver disease (e.g., cirrhosis caused by alcoholism, hepatitis C), acute liver failure, and primary biliary cirrhosis or primary sclerosing cholangitis as well as for nonalcoholic cirrhosis and hepatic or biliary malignancy.

Biliary atresia (bile ducts not formed normally) is the most common indication for pediatric liver transplantation. Five hundred pediatric liver transplants are performed annually; more than half are for biliary atresia. Other indications include neonatal cholestasis (children born with liver failure for unknown reasons), metabolic error leading to liver failure, acute liver failure for any reason (e.g., viral infection, drug overdose, tumor, cirrhosis).

Theoretically, anyone with advanced, irreversible liver disease with certain mortality may be considered for a liver transplant provided the disease can be corrected by liver transplantation (Table 21-5).

Hepatitis B is not eliminated by transplantation, but its recurrence and the damage it can cause may be substantially reduced by giving the client hepatitis B globulin. Hepatitis recurs in the transplanted liver in 80% to

90% of cases, but the damage to the new liver is slow, so many years of symptom-free living can occur.

With the exception of metastatic malignancy and hepatic lymphoma, there are few absolute contraindications to liver transplantation. Liver transplantation for large primary liver cancers is very limited; transplantation remains the best treatment for small tumors (less than 5 cm) in a liver that is already cirrhotic.³³⁷

People with metastatic disease that has spread to the liver are no longer treated with liver transplantation because of the poor outcome. The exception is a small group of people whose liver cancer is characterized by neuroendocrine tumors that are very slow growing. The results of transplantation in this group are not as good as for those individuals with benign disease but acceptable enough to qualify for transplantation.

Some metabolic disorders (e.g., familial hypercholesterolemia) that arise in the liver but produce damage elsewhere in the body can be cured if the liver is replaced with a liver from a normal individual. Many inborn errors of liver metabolism are benign and are not associated with end-stage liver disease. Acute fulminant liver failure secondary to severe hepatitis owing to a virus, toxin, or poison can be life threatening and requires liver transplantation to prevent death.

Transplantation Candidates

The decision to perform a transplantation may be determined by how long the procedure will extend the candidate's life. In general, people with nonmalignant, nonalcoholic liver disease between ages 2 and 60 years are considered most suitable. A definite age cutoff has not been determined; although many transplantation centers do not accept most people as candidates if they are older than 60 years, this limit is being expanded. Older people may be unable to survive the procedure, and clients with considerable damage to other major organs (e.g., heart, lungs) cannot handle the stress of the surgery. For technical reasons, with small birth weight infants surgeons may prefer to wait until significant growth has occurred.

The potential candidate with an end-stage liver disease that is correctable by a liver transplant must also be a good operative candidate. Many potential risk factors have been reported to increase the risk of transplantation (Table 21-6). Clients with alcoholic cirrhosis may be required to remain abstinent 6 months before the transplant, although it has been suggested that liver transplantation itself contributes to recovery from alcoholism.

The recidivism (relapse) rate following liver transplantation varies in reported studies from 4% to 32%, although the majority of studies report a recidivism rate in the 4% to 9% range.^{229,239} The use of the biologic marker carbohydrate-deficient transferrin to screen for alcoholic relapse has been used for the first time in liver graft candidates but remains controversial.^{25,269}

Transplantation Procedure

The liver from the cadaveric donor is removed through a midline incision from the jugular notch to the pubis including a median sternotomy, with particular care to avoid hepatic injury or portal vein transection. The iliac

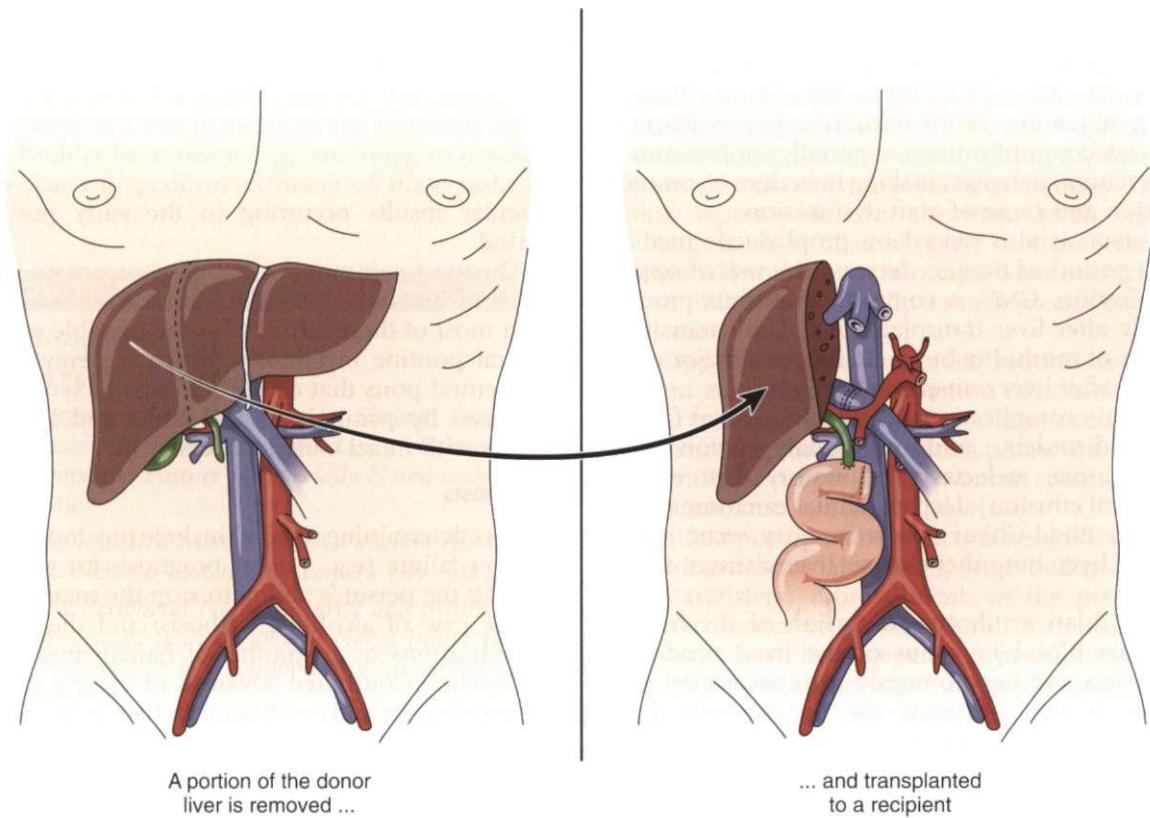
Table 21-5 Liver Transplantation

Indications	Possible Contraindications
Primary biliary cirrhosis	Sepsis
Neoplasm (selected cases)	Hepatic lymphoma
Acute fulminant liver failure	AIDS
Inborn errors of metabolism	Poor client understanding
Alcoholic cirrhosis after documented treatment and recovery	Alcoholic cirrhosis (documented continued abuse)
Drug-induced liver disease	Cirrhosis secondary to drug abuse
Chronic active hepatitis	Chronic active (type B) hepatitis
Neonatal cholestasis (bile suppression)	Advanced cardiopulmonary disease
Biliary atresia	Inability to follow up with treatment
Sclerosing cholangitis	
Budd-Chiari syndrome	
Congenital hepatic fibrosis	
Cystic fibrosis	

Table 21-6 Liver Transplant Risk Factors

Low	Intermediate	High
Increasing age	Active extrahepatic infection	More than one other failing organ
Severity of liver dysfunction in otherwise stable person without encephalopathy	Hepatobiliary sepsis	Prolonged, severe coma
Previous abdominal surgery	Hepatorenal syndrome	Preoperative hemodynamic instability
Preexisting thrombotic disorder	Small-sized infant	Extrahepatic malignancy
	Short-duration coma	Immunosuppressive disorders
	Transplantation across ABO barrier	
	Previous portosystemic shunt	
	Portal vein thrombosis	
	Operative variable	

Reprinted from Meyers WC, Jones RS: *Textbook of liver and biliary surgery*, Philadelphia, 1990, Lippincott, p 406.

**Figure 21-11**

In a minimally invasive live-donor liver transplant, an incision is made just under the donor's rib cage. A portion of the liver is removed; the donor's liver will grow back to a normal size within a few weeks. For the recipient, the diseased liver is removed through an incision in the upper abdomen. The donor liver is placed into the abdomen and blood vessels are reattached to the new liver. The bile duct of the donor liver is attached to the recipient's bile duct or to a segment of intestine so the bile can drain into the small intestine.

artery and vein are also harvested in the event that vascular reconstruction is required.

Living related transplantation requires a much less extensive operative opening, and the reduced-size graft is usually taken from the donor's left lobe (Fig. 21-11). In some situations (e.g., presence of metabolic abnormalities), the autologous graft is placed in an anatomically altered site, thereby preserving the orthotopic position for future use in the case of graft failure; this technique is not possible with disorders leading to portal hypertension.

Successful engraftment of the donor organ requires a recipient hepatectomy to remove the diseased liver, a procedure that can be difficult when there is severe portal hypertension and excessive collateral formation. In many centers the recipient is placed on heart-lung bypass to avoid congestion of the portal circulation and improve venous return to the heart during implantation, thus improving hemodynamic stability.

The implantation procedure begins with anastomoses, that is, surgical formation of a connection between the donor and the recipient's suprahepatic and then infrahe-

patic vena cava. Alternatively, the donor vena cava can be anastomosed side to side with the recipient vena cava if it is left in situ during the recipient hepatectomy (piggy-back technique). The operation then proceeds to the portal anastomosis. After all venous connections, the liver is reperfused.

Complications

Transplantation of the liver differs from renal, lung, or heart transplantation because there is no intervening assistance from an artificial liver; the technical aspects of liver transplantation require precise connection of the hepatic artery, hepatic and portal veins, and the bile duct. In the case of a living donor, there is a risk of hemorrhage and death if an artery is accidentally severed.

Rejection is the most common cause of liver dysfunction after transplantation, most likely after the first week and during the first 3 postoperative months. As with all organ transplantation procedures, the chance of organ rejection requires the use of immunosuppressants with their associated complications, especially suppression of the body's natural defenses, making infections a common complication and cause of graft dysfunction.

Each person is also placed on prophylactic medications for a period of time to decrease the risk of opportunistic infection. CMV, a common infectious process, occurs early after liver transplantation. CMV remains a major cause of morbidity but is no longer a major cause of mortality after liver transplantation.

Extrahepatic complications may include renal failure, neurologic disorders, and pulmonary involvement (e.g., pneumonia, atelectasis, respiratory distress syndrome, pleural effusion). Hepatocellular carcinoma, hepatitis B, and Budd-Chiari syndrome may recur in the transplanted liver, but other chronic liver diseases do not recur.

In Budd-Chiari syndrome, occlusion of the hepatic veins impairs blood flow out of the liver, producing massive ascites and hepatomegaly. It is associated with any condition that obstructs the hepatic vein (e.g., abdominal trauma, use of oral contraceptives, polycythemia vera, paroxysmal nocturnal hemoglobinuria, other hypercoagulable states, congenital webs of the vena cava).

Mechanical postoperative complications include biliary strictures; nonfunction of the graft (i.e., the transplanted liver does not function); hemorrhage; and vascular thrombosis of the hepatic artery, portal vein, or hepatic veins. Mononeuropathy of the ulnar nerve occurs in approximately 10% of orthotopic liver transplantation, primarily attributed to intraoperative compression or postoperative trauma. Other upper extremity mononeuropathies may occur as a result of vascular cannulations (flexible tube inserted to deliver medication or drain fluid).⁵⁵

Other clinically significant neurologic events occur in a substantial percentage of adult liver transplant recipients. Central nervous system complications after liver transplantation may be a consequence of liver disease itself, may be caused by the adrenergic effects of immunosuppressants (e.g., FK506, cyclosporine A), or may result from a wide array of metabolic abnormalities or

Box 21-9

CENTRAL NERVOUS SYSTEM COMPLICATIONS OF LIVER TRANSPLANTATION

- Focal seizures
- Encephalopathy
- Central pontine myelinolysis
- Hemorrhages, infarcts, or both (intracranial, intracerebral, subarachnoid)
- Confusion
- Coma
- Psychosis
- Cortical blindness
- Quadriplegia
- Tremors
- Alzheimer type II astrocytosis
- Central nervous system aspergillosis (fungal infection)
- CMV (viral infection)

vascular insults occurring in the early postoperative period.

The most common central nervous system lesions are listed in Box 21-9. The therapist is likely to be familiar with most of these terms, with the possible exception of central pontine myelinolysis, which is demyelination of the central pons that causes a locked-in syndrome characterized by paralysis of the limbs and lower cranial nerves with intact consciousness.

Prognosis

Factors determining survival include the underlying cause of liver failure (e.g., poorer prognosis for advanced cirrhosis); the person's ability to stop the intake of alcohol in the case of alcoholic cirrhosis; and the presence of complications or symptoms of hematemesis, jaundice, and ascites. Continued advances in the use of immunosuppressant-steroid combinations have increased survival rates through effective immunosuppression with minimal toxicity.

In the case of liver transplantation, survival rates correlate with the number of liver transplantation procedures performed in transplantation centers. Overall 1-year survival rates have improved from 70% 10 years ago to more than 85% in many high-volume centers.⁵⁷ Survival after emergency liver transplantation for acute liver failure is less because such clients are seriously ill at the time of the operation.

The expected 1-year survival rate after a second or subsequent liver transplantation is about 50%. Two groups of people qualify for liver retransplantation: those with serious postoperative complications because of mechanical failure or rejection and those who have a slow, progressive course of chronic hepatic dysfunction, usually caused by rejection or recurrence of primary disease. A model to estimate survival after retransplantation of the liver is being developed to help identify individuals with a poor expected outcome; this information could be useful in further refining candidate criteria selection.¹⁹⁹

Future Trends

Current animal research is centered on identifying and harvesting specific stem cells from the bone marrow that, under special conditions, will convert into functioning liver tissue.²⁴⁸ In human research, a new procedure called *hepatocyte transplantation* is being pioneered. In this procedure billions of donor liver cells are injected by intravenous infusion into the blood with the hope that the cells will correct life-threatening liver problems that would otherwise require a liver transplant.^{122,264}

Other research efforts are working toward the development of bioartificial devices for liver support. An effective temporary extracorporeal liver support system could improve the chance of survival with or without transplantation as the final treatment.¹⁰⁷ Bioartificial liver systems have been tested in human beings with acute liver failure but are not available for general use yet. No device has been developed that can perform all the necessary functions of a healthy liver; researchers are trying to develop liver cells that will perform as many of these tasks as possible.⁶¹

SPECIAL IMPLICATIONS FOR THE THERAPIST 21-3

Liver Transplantation

PREFERRED PRACTICE PATTERNS

4A, 4B: Prevention/Risk Reduction for Skeletal Demineralization Associated with Long-Term Use of Immunosuppressants; Impaired Posture is Especially Noted with Liver Transplantation

5C, 5D, 5E: Impaired Motor/Sensory Function Associated with Central Nervous System Involvement (see Box 21-9)

5F: Impaired Peripheral Nerve Integrity and Muscle Performance Associated with Peripheral Nerve Injury (*ulnar nerve mononeuropathy is a common surgical complication in this population*)

6A, 6B, 6C, 6F: Prevention/Risk Reduction for Cardiovascular/Pulmonary Disorders; Impaired Aerobic Capacity/Endurance Associated with Deconditioning; Impaired Ventilation and Respiration (complications of treatment, especially pneumonia)

The majority of transplanted livers begin to function well within minutes to hours after the vascular clamps are released. The client must be closely monitored for signs of respiratory compromise, bleeding, infection, rejection, and fluid or electrolyte imbalance (see Chapter 5). Vital signs must be monitored as activities are slowly resumed with physician approval and according to the client's tolerance levels (see Appendix B).

Acute Care Phase

Postoperatively, the client will have multiple intravenous lines, drains, and a Foley catheter as well as a painful abdomen with a large abdominal incision and a 4- to 5-inch left axillary incision (bypass procedure) restricted by staples and dressings. Standing postoperative orders are usually followed in the ICU.

The typical ICU stay is 24 to 48 hours, with ventilatory support for the first 24 hours. The patient must relax and let the machine breathe for him or her. The patient cannot talk and may be very anxious. The staff should make every effort to inform the patient regarding what is going on and help the patient communicate.

The large incisions are contraindications for resistive exercises; gradual low-resistance training can be introduced according to the physician's protocol. Physical therapy orders for "out of bed" begin by postoperative day 1. The therapist can assess joint motion, observe for thrombosis or infection, begin thrombosis prevention, and take a look at potential discharge needs.

Any signs or symptoms of infection should be reported immediately. This may include headache, fever, skin rash or red streaks, change in pulse rate, confusion, burning with urination, or other constitutional symptoms (see Box 8-1). Mild signs and symptoms of rejection are present during the first few days to weeks but are controlled in most cases. The patient may report pain over the liver, fever, fatigue, and change in color of stool (gray) or urine (tea color). In terms of morbidity or mortality after liver transplantation, infection is usually a much greater concern than rejection.

Upper extremity range of motion exercises and client education for prevention of adhesive capsulitis (i.e., frozen shoulder) are important concerns. Coughing and deep breathing with a pillow splint are taught early. These people do not want to cough, and respiratory infection is a hazard to avoid.

Often postoperative ascites is a significant problem, making functional training (e.g., bed mobility training, transfers) more difficult in the presence of an altered center of gravity. Hand, pedal and, in men, scrotal edema from dependent positioning frequently develops, requiring active range of motion and bed mobility training as soon as possible.

Assisted ambulation should occur as soon as the client is stable in the upright position; placement of the gait belt can be problematic because the T-tube to drain bile is placed in the right lower abdomen and should be avoided. Try using the gait belt around the upper trunk instead.

Once the telemetry is removed, rehabilitation can progress rapidly. Ascites and associated edema usually resolve within 3 to 4 weeks, but if edema persists, comprehensive lymphedema therapy may be required (see discussion in Chapter 13).

Outpatient Phase

Outpatient therapy continues for approximately 8 weeks postoperatively. The liver transplant recipient with healthy heart and lungs can usually function well at home and resume independent ADLs. Rest and energy conservation balanced with nutrition, exercise, and correct, consistent, lifelong drug self-administration are all considered important features of the rehabilitation process.

Continued.

Pretransplant hepatic encephalopathy usually resolves slowly in the posttransplant period if the donor organ is functioning well; client and therapist will see a reduction or cessation of associated signs and symptoms.

Common problems during the outpatient phase are centered around balance and coordination. Fatigue and reduced endurance add to the client's instability. Sleep disturbance may occur as a side effect of medications contributing to fatigue.

The therapist must be alert to any self-medicating or use of over-the-counter drugs by the client; the client should be encouraged to check with the physician before continuing unmonitored drug use. Steroid usage in older women can cause posttransplant mental confusion; the woman may become uncooperative and disoriented to time and place and experience hallucinations.²⁸¹ Observe for steroid myopathy in all recipients (see Table 5-5).

The abdominal scar may result in a kyphotic posture and altered breathing. Some people continue to use an assistive device. The therapist may be able to assist in improving posture, strength, balance, coordination, and fatigue levels. Exercise is an extremely valuable part of the postoperative recovery phase.

Exercise

Extreme weakness and fatigue reducing clients' activity level are common in many liver transplant candidates with chronic liver disease. Low $V_{0,\text{max}}$ is common in pretransplant liver candidates with primary biliary or alcoholic cirrhosis along with alcohol-induced myopathy contributing to exercise limitations.

Improvement in exercise capacity with training before transplantation has been demonstrated, and new studies confirm the same outcome after liver transplantation on physical fitness, muscle strength, and functional performance in candidates treated for chronic liver disease (see also the section on Exercise, Activity, Sports, and Organ Transplantation in this chapter).^{27,28}

Compliance with a home program of exercise and activity may be a problem; fatigue and quality of life are cited most often for poor adherence. Education is the key since both of these symptoms can be improved with exercise.^{179,325}

The liver plays an important role in providing glucose for oxidation and the maintenance of glucose homeostasis during physical exercise. Denervation of the liver does not alter the release of glucose during physical activity. Consequently, liver transplant candidates can perform quite heavy exercise and maintain acceptable glucose levels.

Heart Transplantation

Overview

In 1905, Drs. Carrel and Guthrie began to perform experimental procedures to prove heart transplantation was possible. In 1946, Dr. Demikhov performed the first heterotrophic heart transplantation in a dog. In 1960, Lower

and Shumway developed the technique for heart transplantation that remains the basis of standard clinical surgical transplantation technique worldwide. The first human heart procedure was performed in South Africa by Christiaan Barnard (1967), followed shortly by the first U.S. transplant by Norman Shumway at Stanford in 1968.¹⁰⁴ To date, over 40,000 individuals have undergone heart transplantation in the United States.³¹⁶

Heart transplantation has been *heterologous* (i.e., from a nonhuman primate, a procedure that is no longer performed) or, more commonly, *homologous* (allograft) (i.e., from another human being). Future trends may develop the *heterologous* transplantation or xenograft (transplantation from other species, such as the pig); see the previous section on Xenotransplantation in this chapter.

Incidence

In the past decade there has been a decline in the number of people listed for heart transplantation as well as a decrease in the number of transplantation procedures performed. In 2004 there were just over 2000 heart transplantation procedures done, with approximately 250 of these cases being children. At present there are over 20,000 individuals alive because of a heart transplantation procedure.

The decline in candidates waiting is due to multiple factors, including improvement in the medical and surgical management of coronary artery disease. The waiting list has also declined because there are fewer people who have been classified as a status 2 being activated in the UNOS list. This is partly due to the fact that the data do not support the efficacy of organ allocation to this group of individuals, and the increase in organ sharing allocates the donor organs to sicker recipients who are listed as status 1A and 1B.³¹⁶

There has been an increase in the number of women awaiting transplantation, number of people waiting with a diagnosis of cardiomyopathy, and the number of individuals waiting for heart transplantation due to congenital defects.³¹⁶

Indications

Potential candidates of cardiac transplantation must have end-stage heart disease with severe or advanced heart failure (New York Heart Association class III or IV end-stage heart disease) to be considered for a donor heart. In the United States, the most common underlying causes of heart failure leading to cardiac transplantation are ischemic coronary heart disease and cardiomyopathy. Cardiomyopathy is a general term that can include ischemic and nonischemic causes for myocardial dysfunction.

Other less common cardiac diseases that may be treated with heart transplantation include sarcoidosis, restrictive cardiomyopathy, hypertrophic cardiomyopathy, congenital heart disease untreatable by surgical correction or medical treatment, and valvular heart disease when the risk of cardiac surgery is prohibitively high.

Transplantation Candidates

The selection of candidates for heart transplantation involves the use of multiple prognostic variables (Box 21-10; see also Box 21-5) in conjunction with medical

Box 21-10**INDICATIONS AND REQUIREMENTS FOR HEART TRANSPLANTATION**

- Cardiogenic shock or low cardiac output state requiring mechanical support
- Low cardiac output or refractory heart failure requiring inotropic support
- End-stage heart disease with NYHA class III and IV not responding to medical intervention
- Life expectancy <50% expected survival at 1-year that includes:
 - Left ventricular dysfunction with ejection fraction <20%
 - Maximal VO_2 treadmill <14 ml/kg/min
 - Peak VO_2 <10 ml/kg/min
 - Ventricular arrhythmias not responsive to medical therapy
 - Cardiac index <2.0 l/min
 - Pulmonary capillary wedge pressure >16 mm Hg
- Age typically <65 years old
- No irreversible pulmonary hypertension
- No other irreversible organ dysfunction
- Free of cancer (time of remission depends on cancer type)
- Free from substance abuse (minimally >6 months)
- Diabetes mellitus with peripheral end-stage organ complications
- No active infection
- Good compliance
- HIV negative status
- Psychological stability
- Financial support
- Family support

urgency criteria established through UNOS status listings (see Box 21-4). People accepted as candidates for heart transplantation are expected to have a limited survival if they do not have surgery.

Pediatric listings differ slightly. Status 1A characterizes a child less than 6 months of age with pulmonary arterial pressure greater than 50% of systolic pressure and life expectancy less than 14 days. Status 1B indicates growth failure in a child under 6 months of age with a pulmonary arterial pressure less than 50% of systolic pressure. Status 2 and 7 are the same for children and adults.

Risk factors in the adult heart transplant candidate must be assessed to provide guidelines about the timing of placing a person on the UNOS waiting list and when to perform the transplantation. The measure of peak exercise oxygen consumption (peak VO_2) has become an indicator of prognosis in advanced heart failure and is currently being used as a major criterion in many centers for the selection of candidates for heart transplantation.

Individuals with peak VO_2 less than 14 ml/min/kg have a lower survival rate unless treated successfully with transplantation. However, VO_2 can be affected by age, gender, muscle mass, and conditioning status. The multiple factors that affect peak exercise capacity may explain why some people with congestive heart failure and a peak VO_2 of less than 14 ml/kg/min have a favorable prognosis even when transplantation is deferred.^{23,47,257}

Ejection fraction and capillary wedge pressure are also used to assess risk. Anyone with an ejection fraction of

less than 20% is also considered a potential candidate for transplantation. Ejection fraction is the amount of blood the ventricle ejects; the normal ejection fraction is about 60% to 75%. A decreased ejection fraction is a hallmark finding of ventricular failure.

Other selection criteria are being debated, such as the issue of transplantation in anyone with diabetes. Currently, most centers accept candidates with well-controlled diabetes who have no microvascular disease; some of the larger centers may consider an individual who presents with mild complications of diabetes.

Age cutoff is also controversial; although the upper age limit for transplantation candidates has been 55 to 65 years, some centers are now willing to transplant hearts or combined heart-kidney transplants into older people who are healthy in all other respects. Age limits for combined organ transplantation are more stringent, with a cutoff age at 50 to 55 years.

The average wait (median) for heart transplantation is between 150 to 180 days for a status 1 candidate. During this wait period the candidate may suffer the progression of the heart failure or the onset of new medical issues, which may complicate the transplantation procedure and negatively impact outcomes.

Despite the decline in individuals waiting for a heart transplant, the supply of donor hearts is limited. UNOS reported that the death rate for potential candidates waiting is 156 deaths per every 1000 patient years. Women die more often than men, possibly because of delayed diagnosis and more advanced heart disease at the time of diagnosis.³¹⁶

Transplantation Procedure

To perform a transplantation, the autonomic nervous system is surgically disconnected to remove the diseased native heart. The autonomic nervous system is not reconnected at the time of the donor heart implantation. This leaves the transplant recipients with the loss of the fight-or-flight response. The heart relies on the intrinsic properties of the heart for sufficient contractility and cardiac output.

In general the recipient will have an elevated heart rate at rest due to the loss of the parasympathetic input, a decrease in compliance (the heart's ability to relax to completely fill), and a blunted heart rate response with exertion due to the loss of the sympathetic nervous system. The heart relies on the release of catecholamines to increase rate and contractility, and there is a delay in recovery. In general, the recipient has an exercise capacity of 65% to 70% of predicted VO_2 capacity.¹³⁴

Almost all heart transplantations done at this time are *orthotopic*; that is, the diseased heart is removed and the donor heart is grafted into the normal anatomic site. There are three surgical procedures that can be used to implant the heart: biatrial, bicaval, and total procedure. The biatrial procedure involves suturing the new heart on the native atrial wall. This procedure is not used as much anymore due to the increased incidence of arrhythmias and valvular dysfunction when compared with the other two procedures. The bicaval procedure is the most common at this time and involves the anastomoses of the superior and inferior venae cavae. The total procedure

includes the bicaval approach plus the anastomosis of the pulmonary veins.^{115,266}

In the *heterotopic* cardiac transplantation, the recipient's diseased heart is left intact and the donor heart is placed in parallel with anastomoses between the two right atria, pulmonary arteries, left atria, and aorta. In the heterotopic transplantation, the donor heart assists the diseased heart. This type of procedure accounts for less than 1% of the transplantation population and may be performed in an individual with fixed pulmonary hypertension or someone who is physically very large, requiring a higher cardiac output than a donor heart from an average-size donor.

Complications

One of the most common posttransplant complication is rejection. With the increased understanding of the immune system there has been a decrease in hyperacute rejection. This type of rejection occurs within minutes to hours postimplantation and involves a catastrophic immune response from the interaction between the recipient's circulating antibodies and donor antigens.^{104,190}

An episode of acute rejection can occur at any time after transplantation but is most common within the first 6 months. Acute rejection can be an antibody-mediated response and/or T cell-mediated response. The antibody-mediated acute rejection occurs early in the postoperative period and is associated with capillary endothelial changes with macrophage and neutrophil infiltrations and interstitial edema.

T cell-mediated rejection is associated with increased lymphocytes and macrophages, which lead to a complex immune response and the activation of cytotoxic T cells, B cells, and natural killer cells, resulting in the destruction of interstitial and vascular graft tissue.^{134,190,261} The recipient may present with variable signs and symptoms, including malaise, fever, alteration in heart rate or arrhythmias, decreased exercise tolerance, and heart failure. The recipient may also be totally asymptomatic.¹³⁴

Transplant Coronary Artery Disease (Allograft Vasculopathy). The third type of rejection is chronic rejection, which can present as a medical issue months to years posttransplant. In the heart transplant recipient, chronic rejection presents itself as coronary arterial vasculopathy.

Chronic rejection is associated with both humoral and cellular acute rejection, leading to a diffuse proliferation of smooth muscle cells, concentric intimal narrowing, and accelerated diffuse obliterative atherosclerosis of both intramyocardial and epicardial arteries and veins (Figs. 21-12 and 21-13).

Chronic rejection, or coronary arterial vasculopathy, is associated with prolonged ischemia at the time of transplantation, severity and frequency of acute rejection, diabetes, smoking history, and CMV.^{90,116} Recipients who are suffering from chronic rejection may initially be asymptomatic, but as the disease progresses the recipient will present with signs and symptoms of heart failure.

It is atypical for the patient to experience any angina symptoms despite the atherosclerosis and decreased myocardial perfusion because of the lack of autonomic nervous system innervation. There have been case reports

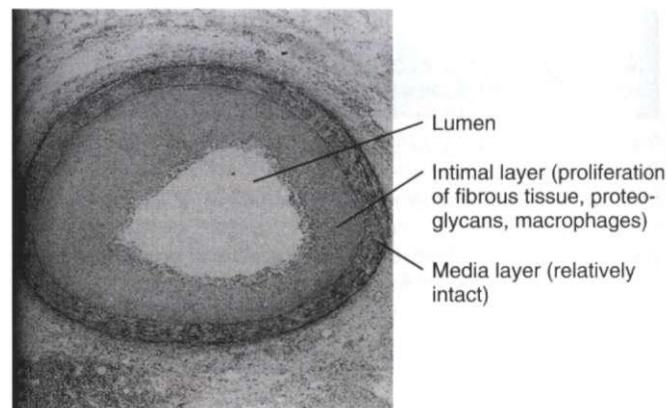


Figure 21-12

Transplant coronary artery disease. Proliferation of the intimal layer of the epicardial coronary artery from a 14-year-old cardiac transplant recipient 1 year after transplant. This condition produces a significant reduction in diameter of the arterial lumen that will compromise blood flow to the myocardium. (Reprinted from Gajarski RJ: Update on pediatric heart transplant: long term complications, *Tex Heart Inst J* 24[4]:260-8, 1997.)

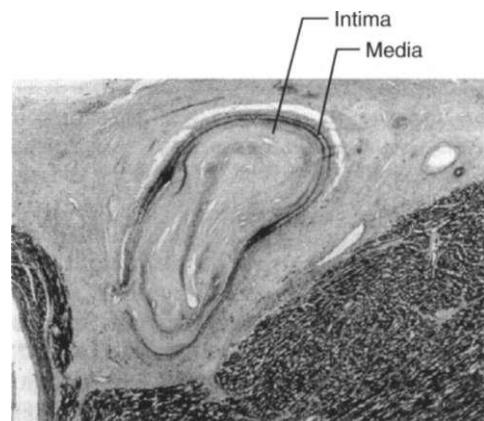


Figure 21-13

Transplant coronary artery disease resulting in complete occlusion of epicardial coronary artery in an 11-year-old heart transplant recipient 4 years after transplantation. The lumen is obstructed with dense fibrous tissue with thinning and fibrosis of the media layer. (Reprinted from Gajarski RJ: Update on pediatric heart transplant: long term complications, *Tex Heart Inst J* 24[4]:260-8, 1997.)

that some recipients present with angina-like symptoms leading to the diagnosis of vasculopathy and the conclusion that, to some degree, there is reinnervation of the sympathetic nervous system.

These reports are supported by the fact that 2 to 4 years posttransplant, the recipient has an increase in heart rate response during exercise and a quicker recovery, which suggest some recovery of the autonomic nervous system. Therefore it is important that transplant recipients undergo routine testing to rule out myocardial ischemia related to vasculopathy.^{21,134}

Infection. As the transplantation team manages the immunosuppressive medications to minimize the incidence and severity of rejection, the risk of infection increases. Infections account for approximately 20% of deaths within the first year.¹⁹²

The characteristics of infection in the transplant recipient can be classified in several ways. Infections can be classified in relation to the time of transplant. Infections occurring within the first month may be (1) related to unresolved infection of the recipient prior to transplant and exacerbated by the surgery and the immunosuppressive therapy; (2) transmitted from the donor; and (3) perioperatively related to the medical and surgical procedure, including line, wound, and pulmonary infections (most common).

These infections are most commonly caused by bacteria, hepatitis, and herpes simplex virus. Infections are most common between 1 and 6 months posttransplant, usually related to a prior infection that has not resolved within the first 30 days. There is an increased incidence of viral infections including CMV, tuberculosis, EBV, and opportunistic infections that include *Pneumocystis carinii* pneumonia, and fungal infections such as Candida and Aspergillus.

After 6 months, complications related to infections are typically associated with community-acquired infections such as influenza and respiratory syncytial virus. CMV continues to be a concern. CMV is associated with infection, and there is an increase in acute and chronic infection in recipients who are positive for CMV, particularly if there is a mismatch between the recipient and donor. The highest risk of complications from CMV occurs when the recipient is seronegative and the donor is positive.^{134,201}

Acute Graft Failure. In the early postoperative phase, the donor heart may not sufficiently support the circulatory demand of the body and is associated with early morbidity and mortality. The dysfunction of the graft may be related to an ischemic injury sustained in the procurement process. There may be a reperfusion injury sustained at the time when the circulation is reestablished through the donor heart. Finally, graft dysfunction may be the result of acute right ventricular failure because the right ventricle is not accustomed to contracting against the elevated pulmonary arterial pressures within the recipient's pulmonary vascular resistance.¹³⁴

Neuromuscular. Reports have also been made of generalized polyneuropathy accompanying solid-organ rejection of the heart and kidneys. The neuropathy affects proximal and distal muscles and demonstrates hyporeflexia or areflexia.

Musculoskeletal. There is a decrease in muscle mass and strength due to the effects of immobility, chronic effects of the inflammatory response, and effects of immunosuppressive medications. Tacrolimus and cyclosporine inhibit and transform myosin heavy chain and oxidative enzymes from fast to slow muscle twitch. There is also a decrease in skeletal muscle perfusion due to the increased sensitivity of peripheral chemoreceptors.⁶⁴

Osteopenia and osteoporosis are significant complications for transplant recipients of all ages. Osteopenia has been reported to affect 20% to 49% of candidates waiting for transplantation, and 14% have evidence of vertebral compression fractures. Posttransplantation, the risk of bone disease increases with the use of immunosuppressive medications and renal dysfunction. Corticosteroids stimulate an increase in osteoclastic activity and have

adverse effects on skeletal muscles that further contribute to decreased bone density.

The effects of calcineurin inhibitors are still unclear, but in animal models it appears that they increase the rate of bone turnover, with the bone reabsorption rate being greater than the rate of bone formation. Tacrolimus and cyclosporine also have adverse effects on skeletal muscles.^{37,193}

Cancer. The incidence of cancer is proportional to the drug levels of the immunosuppressive medications; in general, average onset is between 2.5 and 4 years posttransplant. Skin cancer is the most common form of cancer (basal cell more often than squamous cell carcinoma).

With heart transplant recipients there is a higher incidence of lymphomas related to high drug levels and the use of OKT₃. Posttransplant lymphoproliferative disease (PTLD) is associated with EBV, which causes a proliferation of B cells; more recently, however, there appears to be an association with EBV and T-cell proliferative lymphomas. In the early posttransplant phase PTLD may begin in the donor organ; it is important to differentiate PTLD from rejection. PTLD may also present in extranodal sites such as the lung, gut, or central nervous system as well as a disseminated disease.^{192,244,258,298}

Other. Other complications occur as a result of long-term use of immunosuppressive medications and their adverse effects (see the section on immunosuppressants in Chapter 5). It has been reported that 50% to 95% of recipients will be treated for hypertension due to medications and renal insufficiency. Sixty to 80% of recipients will have hyperlipidemia, and approximately 35% to 40% will develop diabetes.

One third of recipients will have renal dysfunction, with approximately 5% to 8% progressing to ESRD and requiring hemodialysis or renal transplantation.^{134,192} Cyclosporine- or tacrolimus (FK506)-induced hyperuricemia, along with renal insufficiency and use of loop diuretics, can lead to an increase in gout.

Gout is characterized by early symptoms, including arthralgias and monoarthritis affecting the first metatarsophalangeal joint, knees, ankles, heels, and insteps. Over time, upper extremity joints become involved, progressing to polyarticular chronic arthritis. Treatment is as for primary gout (see Chapter 27).

Gastrointestinal problems are especially prevalent after lung transplantation and heart-lung transplantation, and less often after heart transplantation. Problems range from major (diverticulitis, perforation, and malignancy) to minor (polyps, pseudo-obstruction, and benign anorectal disease).¹¹³

Finally, 25% of recipients will need to be treated for depression. There have been reports that approximately 10% of recipients suffer from FTSD.^{102,116,192}

Prognosis

The International Society of Heart and Lung Transplantation reports over 66,000 heart transplant procedures; there were approximately 19,000 recipients alive in the United States in 2004. In general, people tolerate the transplantation procedure well, and the graft resumes normal function promptly.

Recipients are often extubated and out of bed into a chair 1 to 2 days after surgery. Survival times were short 30 years ago, but new immunosuppressive drugs developed in the mid-1980s and improved in the 1990s, more careful candidate selection, endomyocardial biopsy to allow for early rejection detection, and advanced medical-surgical techniques have contributed greatly to improved longevity.

Only a decade ago, infection and acute and/or chronic rejection were the major causes of death in heart transplant recipients. With improved longevity, chronic graft vasculopathy (accelerated atherosclerosis, transplant coronary artery disease) and malignancies are now the primary causes of death among heart transplant recipients. Infection, rejection, and sequelae of long-term immunosuppression (especially renal insufficiency or renal failure) remain the primary treatment issues.

UNOS reports continued improvement in the survival rates after cardiac transplantation. Survival rates are excellent, with a 3-month survival rate of 92% and 1-year, 3-year, and 5-year survival rates of 87.5%, 78.4%, and 71.5%, respectively.

There are several factors that contribute to survival rates. Individuals who undergo transplantation due to cardiomyopathy have a higher survival rate than patients with ischemic heart disease. Retransplantation still has the lowest survival rate at 57%.^{3,6} Caucasians have the highest survival rates, with African-American recipients having an approximately 10% lower 5-year survival rate. Adolescent recipients also have 5-year survival rates below 70%, and women have a 5% lower 5-year survival rate than men.^{134,316} Although data are limited on the long-term success of heart transplantation, nursing homes are now receiving organ transplant recipients as residents.⁹⁹

Future Trends

Artificial heart devices (e.g., AbioCor system [ABIOMED, Danvers, Mass.], CardioWest total artificial heart [SynCardia Systems, Inc., Tuscon, Ariz.]) are a possible alternative to VADs. Individuals who have both right- and left-sided heart failure or who have other problems that limit the use of left VADs may benefit from an implantable artificial heart. The artificial heart is designed to sustain the body's circulatory system and to extend the lives of people who would otherwise die of heart failure.

The first human recipient in 2001 survived 17 months after the artificial heart was implanted. Since then fully implantable artificial heart devices have been approved by the Food and Drug Administration (FDA) under Humanitarian Use Device rules. These devices are intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4000 individuals per year in the United States and for whom no comparable device is available.

The FDA approves a Humanitarian Use Device based primarily on evidence that it does not pose an unreasonable or significant risk of illness or injury to the patient and that the probable benefits to health outweigh the risk of injury or illness from its use; however, the effectiveness of the device for the condition has not been demonstrated.

To date the artificial heart has only been approved for use in cases of end-stage heart failure with irreversible left and right ventricular failure and when surgery or medical therapy is inadequate. Individuals with advanced heart failure who are not eligible for heart transplantation or other treatment and who are not expected to live more than 30 days without intervention may receive an implantable replacement heart.

The anatomic heart is removed during the implantation procedure and replaced with a battery-operated mechanical heart. The internal battery can be recharged through tiny wires from the implant to the surface of the skin. The person can be free from external connections for short periods of time. During sleep the system is plugged into an electrical outlet.

Other research centers on the role of stem cells in cardiac regeneration. After myocardial infarction, injured cardiomyocytes are replaced by fibrotic tissue, promoting the development of heart failure. Cell transplantation has emerged as a potential therapy, and stem cells may be an important source of these cells. Embryonic stem cells can differentiate into true cardiomyocytes, making them a potential source of transplantable cells for cardiac repair.²⁸⁴

SPECIAL IMPLICATIONS FOR THE THERAPIST 21-4

Heart Transplantation

PREFERRED PRACTICE PATTERNS

4C: Impaired Muscle Performance

4G: Impaired joint Mobility, Muscle Performance, and Range of Motion Associated with Fracture (secondary to medications)

5G: Impaired Motor Function and Sensory Integrity Associated with Polyneuropathies (immunosuppressant-induced)

6A: Primary Prevention/Risk Reduction for Cardiovascular/Pulmonary Disorders (for clients who do well posttransplant)

6B: Impaired Aerobic Capacity/Endurance Associated with Deconditioning

6C: Impaired Ventilation, Respiration/Gas Exchange, and Aerobic Capacity/Endurance Associated with Airway Clearance Dysfunction

6D: Impaired Aerobic Capacity/Endurance Associated with Cardiovascular Pump Dysfunction or Failure

7A: Primary Prevention/Risk Reduction for Integumentary Disorders

Pretransplant

The therapist's role in transplantation varies from region to region. In some areas, the therapist is only involved with the pretransplant candidate if that person has been hospitalized. Some therapists will treat these clients in the outpatient setting to address muscle and endurance deficits. Goals are to improve function, either to make them a stronger candidate for transplantation or assist the transplantation team in determining timing for listing or timing for other

medical or surgical interventions. Potential transplant recipients are educated on the role of physical therapy during the pretransplant and posttransplant periods.¹¹⁹

The outpatient pretransplant physical therapy evaluation should include a general assessment of strength, functional mobility, range of motion, balance, and symptom inventory.¹¹⁹ For all therapists working with individuals with heart disease, the 6-minute walk test provides a clinical assessment tool that is useful in developing an effective rehabilitation program and also offers the therapist some guidelines for recommending someone as a potential transplantation candidate.⁵⁴

An individualized home exercise program is provided, including active and/or resistive upper and lower extremity exercises. Increasing the overall activity level is encouraged in any way possible (e.g., walking, stationary biking, swimming). Individuals with chronic heart failure tolerate exercise intervention only when they are well compensated with medications and/or close monitoring.¹¹⁹

Criteria required prior to initiating an aerobic exercise program include (1) resting heart rate below 120 beats/minute, (2) ability to speak comfortably while exercising, (3) respiratory rate below 30 breaths/minute, and (4) reports of no more than moderate fatigue. For inpatients with a pulmonary artery catheter or invasive monitoring, cardiac index must be greater than or equal to 2 l/min/m² or a central venous pressure must be less than 12 mm Hg.⁵¹

Exercise programs for individuals awaiting a heart transplant are designed with the results of each person's evaluation in mind. Maximizing overall strength and endurance within the person's symptoms and tolerance is extremely important to help prevent complications and improve outcomes following surgery. Intensity is largely based on ambulation time and the rate of perceived exertion.¹¹⁹

Side effects of medications contribute to the high incidence of musculoskeletal injuries (e.g., steroid myopathies and neuropathies, avascular necrosis, osteoporosis). Prevention is an important component of the pretransplant habilitation and posttransplant rehabilitation programs. See specific recommendations in the section on Osteoporosis in Chapter 24.

Acute Care Phase

In the acute care setting, immediate postoperative considerations are important. Because most cardiac transplant candidates have experienced months of restricted activity before surgery, airway clearance and general strengthening are important aspects of early treatment.

Physical and occupational therapy initiated in the ICU focuses on restoring mobility and functional skills, increasing strength, and improving balance and coordination; strengthening should be functional in nature and focus on muscles of the lower extremity, pelvic girdle, and trunk. Bed mobility, transfer training, and ambulation can begin as early as postoperative day 1 and progress as tolerated.

Airway clearance and breathing exercises are essential to improve lung volume and prevent atelectasis (particularly left lower lobe atelectasis), especially in the case of implantation of an artificial heart because of the location of the device. Frequent, slow, rhythmic reaching, turning, bending, and stretching of the trunk and all extremities many times throughout the day help alleviate the surgical pain-tension cycle and facilitate pulmonary function.

These exercises should be done within tolerance for each individual. Arms can be raised above 90 degrees in forward flexion. Horizontal abduction out of the frontal plain is contraindicated in anyone who has had an open thoracotomy to avoid "cracking the crab." In this procedure, the rib cage and sternum are lifted perpendicularly as the hood of a car would be lifted, referred to as a "clam shell" or "crab shell." Any motion that can open the incision is not allowed until healing has taken place.

Postoperative reports of chest pain may be due to the sternal incision and musculoskeletal manipulation during surgery. Sternal precautions must be reinforced daily for some patients. Sternal precautions are standard postoperative orders but may vary from center to center (see Box 12-3).

Chest pain secondary to myocardial ischemia or coronary insufficiency does not occur in the early postoperative months because the heart has been denervated. Any other symptoms of ischemia, such as dyspnea, lightheadedness, faintness, or increase in perceived exertion should be attended to and reported. Chest pain may also be associated with postoperative bleeding and pleural effusion.

Progressive ambulation can be initiated as soon as the client can transfer. It is safe to utilize a cardiac or standard walker. If the person has a dysfunctional lower extremity that will require an increase in upper extremity weight bearing, the situation should be discussed with the surgeon. Upper extremity weight bearing may vary based on the surgeon's preference, quality of the bone, placement of the sternal wires, and the comorbidities of the patient.

Ambulation and endurance training (e.g., use of a stationary bike or treadmill) should be progressed as tolerated, meaning stable vitals, including electrocardiogram and good recovery without fatigue carrying over from day-to-day. It is recommended to instruct the person to use the rate of perceived exertion (RPE) scale or Borg scale since heart rate is no longer a viable means to indicate intensity.

The recipient should work at a low to moderate intensity level (2 to 3 out of 10 on the modified RPE or 12 to 13 out of 20 on the RPE scale; see Table 12-13) based on present medical condition and prior level of function.⁵³ Whether to use the treadmill or bicycle is generally an individual decision made by the client based on personal preference; presence of orthopedic problems must be taken into consideration.

Resistive elastic or small weights and aerobic training should be steadily progressed with the increase in resistance, including upper extremity training intro-

Continued.

Table 21-7 Physical Therapy Management

Acute	Outpatient
Progression of functional mobility	Functional assessment 6-Minute walking distance
Sternal precautions	Submaximal graded exercise test
Assess hemodynamic stability (VAD function)	Assess hemodynamic response
Pulmonary clearance	Monitor for hypertension
Monitor INR: 2.5-3.5	Arrhythmias
Monitor driveline site for VAD patients	General strengthening and stretching
Monitor volume/pressure	Assess for signs of rejection and infection
Assess for signs of rejection and infection	Assess for neurologic complications
Assess for neurologic complications	Education and home/community-based exercise program
Education	
Side effects of medications	
Exercise response; pulse monitoring	
Signs of rejection and infection (see Table 21-3 and Box 8-1, respectively)	

duced between 4 and 6 weeks postoperatively. Pushing or pulling activities and lifting more than 10 lbs are contraindicated in the first 4 to 6 weeks, but this may vary from program to program.

The primary physical therapy goals focus on increasing functional mobility and preparing for discharge and include a home exercise program, sternal precautions (see Box 12-3), and a plan for exercise progression (Table 21-7). Client education is a key component of the posttransplant program, and each member of the team must take this role seriously. An excellent summary of acute care and outcomes for cardiac transplantation is available for acute care therapists.⁵³

It is important that the therapist have knowledge of medications and their potential side effects; monitor vital signs; encourage good nutrition, weight management, and good health; maintain pretransplant behavioral changes (including smoking cessation and weight management); and encourage the transplant recipient to continue exercising during the posttransplant period, even during episodes of rejection.

By this time, the client is independent in pulse monitoring, and understands the RPE scale, proper handwashing techniques, and scar management and can demonstrate knowledge of early signs and symptoms of rejection or infection, especially since these clinical manifestations may appear during exercise. The client must know the appropriate action to take should there be any change in health status.

Other therapy program considerations may include balance assessment and falls prevention, spine care, osteoporosis prevention, weight-bearing exercises, and coordination and strengthening exercises as well as a conditioning and aerobic program.

Although assessing work capacity is important, performing an assessment of transplant recipients must take into consideration daily life and daily activities first. Assessing potential return to work and work requirements may occur as early as 3 to 4 months depending on occupation. For more physical jobs work assessment typically does not occur until 6 to 12 months after transplant. The team will assess hemodynamic status; the therapist will make objective assessments of the recipient's hemodynamic responses to activity and exercise. For example, a job that involves lifting requires assessment of cardiovascular compliance and hemodynamic stability during lifting, whereas someone at home must be safe in ADLs.

Exercise

Individuals undergoing heart transplantation, like those undergoing coronary artery bypass surgery, are affected by preoperative inactivity, the adverse systemic effects of heart failure, postoperative deconditioning, and medication effects.

These individuals can benefit greatly from exercise rehabilitation (see also the section on Exercise, Activity, Sports, and Organ Transplantation in this chapter). Heart transplant recipients can experience significant improvements with exercise. Exercise can improve hemodynamics and assist in managing blood glucose level, hypertension, and weight management.

There are also improvements in oxygen extraction and utilization along with increases in muscle strength, bone density, and function. Improvements occur in maximal and peak oxygen consumption with a delay in the anaerobic threshold observed when the recipient participates in a comprehensive program.*

Reasons for low exercise tolerance observed in heart transplant recipients are multifactorial and lead to a decrease in oxygen consumption and work efficiency.

EFFECTS OF DENERVATION

Heart transplantation results in a denervated myocardium and an impaired ability by the autonomic nervous system to regulate cardiac function (Box 21-11). The resting heart rate after transplantation and denervation is higher than normal (usually in the range of 90 to 115 beats/minute); an external pacemaker may be used if there is not an efficient heart rate to sustain cardiac output. Organ denervation and medications delay or blunt an increase in heart rate in response to exercise.

Persisting denervation and sympathetic vasoconstriction inducing functional vascular abnormalities prevent adequate increase in blood flow to exercising limbs and may contribute to decreased exercise performance.²⁶ Residual abnormalities of ventilatory and gas exchange responses to exercise following heart transplantation are also attributed to the chronotropic incompetence associated with denervation.²⁶² Chronotropic incompetence is a term used to describe the reduced heart rate response to exercise in heart transplant recipients.

Box 21-11**EFFECTS OF CARDIAC DENERVATION**

- Heart rate
 - Elevated at rest
 - Blunted rise with exertion
- Stroke volume: blunted rise with exertion
- Cardiac output: 70%-75% of predicted
- VO_2 : 70%-80% of predicted
- Pulmonary arterial pressure
 - Elevated at rest
 - Marked rise with exertion
- Anticipatory effect: lost
- Abnormal diffusion capacity
- Ventilation: increased response to exertion
- Loss of anginal pain as a warning sign of myocardial ischemia during early years of denervation

Clinical Meaning

- Need for extensive warmup
- Decrease in exercise capacity
- Marked blood pressure response
- Rely on other data to detect ischemia

Modified from Braith RW: Exercise training in patients with congestive heart failure and heart transplant recipients, *Med Sci Sports Exerc* 30(10):S367-S378, 1998.

Decreased peripheral blood flow is only one variable to consider. Reduced oxygen extraction and utilization, differences in muscle fiber type, and decrease in oxidative enzymes may also contribute to reduced exercise tolerance.

In addition to reduced cardiac and skeletal muscle performance, it is likely that the mood state of the individual; level of depression and anxiety; and decreases in cognitive function such as attention, concentration, and mental flexibility may affect the person's ability to participate in activity by affecting frequency, intensity, and duration of exercise.⁶⁹

Over time some recipients may regain partial reinnervation, in which case the individual should be able to exercise at higher workloads, have fewer exertional symptoms related to cardiac limitation, and heart rates may surpass 35 beats/minute.¹⁶³ This phenomenon does not happen until late after transplantation, and the magnitude of reinnervation is variable.

Studies show a functional significance during exercise in people with marked reinnervation, including a higher maximal heart rate, increased peak oxygen uptake, increased oxygen pulse, and earlier heart rate recovery after cessation of exercise (and falling more rapidly) than in the nonreinnervated cases.^{163,165,301,313,336}

IMPORTANCE OF WARMUP AND COOL DOWN

In the denervated myocardium, peak heart rate will (on average) only increase 15 to 25 beats/minute from the resting level during moderate to high submaximal exercise. The therapist needs to remember that the recipient is catecholamine dependent, which means a minimal of 5 minutes is needed to warm up and allow the body to release catecholamines. Catecholamines

will allow a minimal increase in heart rate and contractility, thus increasing cardiac output. Exercise should include large muscle groups to promote venous return and thus maximize filling of the ventricles.^{32,213}

If the recipient does not warm up sufficiently, the feeling of fatigue and stress (similar to an athletic "hitting the wall") is experienced due to the inability to increase cardiac output to meet demands. The recipient is functioning in anaerobic metabolism.

Individuals must be monitored for intensity and tolerance according to symptoms and by an RPE scale while working within an acceptable range for heart rate response. The therapist should not expect to see a rise in heart rate more than 35 beats/minute with exertion. If this occurs the person should be monitored closely for rejection.

Although the denervation eliminates the sympathetic and parasympathetic nervous system input to the heart, the Bainbridge reflex, catecholamine response, and Starling's law allow for increased stroke volume. The Bainbridge reflex causes heart rate to increase as venous return to the heart stimulates volume receptors in the atria to trigger an increased heart rate.

Catecholamines such as epinephrine and norepinephrine result in sympathetic stimulation to increase rate and force of muscular contraction of the heart, thereby increasing cardiac output, and to constrict peripheral blood vessels, resulting in elevated blood pressure.

Starling's law states that the greater the myocardial fiber length (or stretch), the greater will be its force of contraction. The more the left ventricle fills with blood, the greater will be the quantity of blood ejected into the aorta. This is like a rubber band: the more it is stretched, the stronger it recoils or snaps back. Thus a direct relation exists between the volume of blood in the heart at the end of diastole (the length of the muscle fibers) and the force of contraction during the next systole.

All of this is to say a strong initial increase in venous return associated with increased activity and large muscle contraction is responsible for early increases in heart rate; within 5 to 6 minutes after warmup, catecholamines are activated and heart rate continues to increase. The heart rate may remain elevated after exercise secondary to remaining circulating catecholamines. A similar catecholamine response is not observed during isometric or isotonic contractions.

With the loss of autonomic nervous system input over time, the ventricles hypertrophy because of a loss of compliance and from working against elevated pulmonary and systemic pressures. This, combined with the reduced cardiac output, altered kidney function, and use of antihypertensive medications, leads to a reduction in cardiac reserve, or the ability to increase output from rest to exertion. This reduced reserve will be most evident during exercise, requiring close monitoring for exertion hypertension.

Continued.

IMPORTANCE OF MONITORING VITAL SIGNS

It is not uncommon to see a change in diastolic blood pressure (+/- 10 to 15 mm Hg) during exertion. Each transplantation center typically has guidelines for blood pressure parameters. In general, an increase or decrease in diastolic pressure greater than 20 mm Hg, a drop in systolic pressure, or rise greater than 180 to 200 mm Hg warrants physician notification and adjustments to workload intensity or duration.

With the loss of vagal innervation, hypotension can be a problem, especially if there has not been an adequate warmup or cool-down period. The physiologic changes unique to heart transplant clients require a thorough warmup before exercise to stimulate catecholamine release (epinephrine, norepinephrine) and to give the heart necessary time to prepare for peak activity. The warmup period should be mild and long in order to prevent oxygen deficiency. Each step in the exercise protocol should be prolonged for up to 5 minutes to allow for a steady state of heart rate.⁵⁴

Likewise, a cool-down period is essential after cessation of exercise to allow for the decrease in blood pressure and return to baseline. The recipient's heart rate can remain elevated for hours due to the loss of parasympathetic input and high levels of circulating catecholamines combined with an adrenergic hypersensitivity.

Following heart transplantation, there may be allograft vasculopathy, a manifestation of chronic rejection, which will cause increasing ischemia of the transplanted heart during increasing activity and exercise. This cardiac allograft vasculopathy can contribute to reduced oxygen uptake and a ventilation/perfusion mismatch, limiting exercise capacity.²⁷⁰

If the recipient has concomitant pulmonary involvement, abnormal diffusion capacities with altered ventilation responses may occur. These pulmonary components can cause a decrease in cardiac function with possible myocardial ischemia.

Although there have been some documented cases of angina, most of these clients will not experience ischemia-induced angina as an early warning sign of cardiac impairment. This is another reason the therapist must follow appropriate exercise guidelines to stimulate a catecholamine response and monitor vital signs to assess cardiac function.

ISOMETRIC EXERCISE

Isometric exercise puts a volume stress rather than a pressure stress on the heart and cannot be graduated. In the acute care phase the recipient's heart is very volume or preload dependent; therefore aggressive isometric exercise will decrease preload and should be avoided at first.

This type of exercise should be initiated only with the physician's approval and performed with extreme caution only after considerable dynamic warmup to raise the heart rate. Once the client has moved past the acute care phase, rehabilitation, including isometric exercise, can be utilized if indicated and progressed as tolerated. In addition, impaired skeletal muscle metabolism and impaired vasodilation in skeletal muscle as

a result of end-stage heart failure present before transplantation is reversed slowly after transplantation; these effects may persist 6 months after transplantation.

Alternate Options: Mechanical Circulatory Support

Cardiac disease is the leading cause of death in the United States, with over 5 million individuals living with heart failure. Cardiac transplantation is a limited option because of the shortage of donor organs, with less than 2500 hearts harvested per year; in addition, not all people with end-stage heart disease are candidates for transplantation.²⁷⁸

As a result, mechanical circulatory support has become an established procedure for bridging people to cardiac transplantation and more recently is under investigation as an alternative to transplantation.³¹⁴ Mechanical circulatory support can be generally classified into three systems. The intraaortic balloon pump (see discussion in Chapter 12 and Fig. 12-14) is primarily used to stabilize a patient's cardiac system by improving myocardial perfusion and decreasing the work of the left ventricle during acute distress. Ten to 20 years ago the intraaortic balloon pump was also used to support a person who had compensated from heart failure and was waiting for transplantation.

Extracorporeal membrane oxygenation (ECMO) is a mechanical circulatory device similar to the cardiopulmonary bypass machine used during open heart surgery. This device will support both gas exchange and circulation for a heart that is poorly functioning. It is typically used when someone has a complication during an open-heart procedure and is placed on ECMO to support the cardiopulmonary system.

Finally, there are several VADs that can be used to support heart function. It is estimated that approximately 50,000 people with heart failure are candidates for VAD support. The term VAD describes any of a variety of mechanical blood pumps used to replace the function of the right or left ventricle or both. Although the first VAD was implanted in 1969, it was not considered a true surgical option for heart failure until 1984, when the first patient was implanted with a VAD as a bridge to transplantation.^{104,129}

Types of VADs. There are several ways VADs can be classified, including length of time their use is intended, how they operate, and how they support heart function. First, there are devices designed to provide acute and temporary support (10 to 14 days). These devices can support the function of the right or left ventricles or provide biventricular support.

These VADs are implanted in emergent situations or when the medical team believes that if the heart is allowed to "rest" it may recover and resume a sufficient function. Bio-Medicus (right ventricle support; Medtronic, Minneapolis, Minn.), ABIOMED (right, left, and biventricle support), and CentriMag (right ventricle support; Thoratec Corporation, Pleasanton, Calif.; Fig. 21-14) are examples of temporary VADs.



Figure 21-14

A, CentriMag is a VAD that is designed to provide emergent and temporary (up to 14 days) right, left, or biventricular support with the goal to achieve hemodynamic stability. **B**, A patient is initiating gait training while being supported by a right VAD (CentriMag), another more long-term left VAD (VentrAssist), and mechanical ventilation. (**A**, Courtesy Levitronix, LLC, Waltham Mass. **B**, Courtesy Chris L. Wells, University of Maryland Medical Center.)

The ability of the rehabilitation staff to mobilize these patients will depend upon two things: the hemodynamic stability and how well the cannulas (conduits that carry blood between the VAD and the body) are sutured to secure the connections between the cannulas and the cardiovascular system.

There are several devices that are designed for longer use such as the Thoratec and HeartMate (Thoratec Corporation, Fig. 21-15), Novacor (WorldHeart, Oakland, Calif; Fig. 21-16), Jarvik (Jarvik Heart, Inc., New York; Fig. 21-17), and VentrAssist (Ventracor Limited, Chatswood, NSW, Australia). (The VentrAssist device has not been approved for clinical use in the United States and is still under clinical investigation.) All of these VADs are designed to support the left ventricle except the Thoratec (Fig. 21-18), which can also support the right ventricle or both.

These devices are implanted when it is determined that (1) the person's heart can no longer support function despite maximal medical intervention, (2) the person

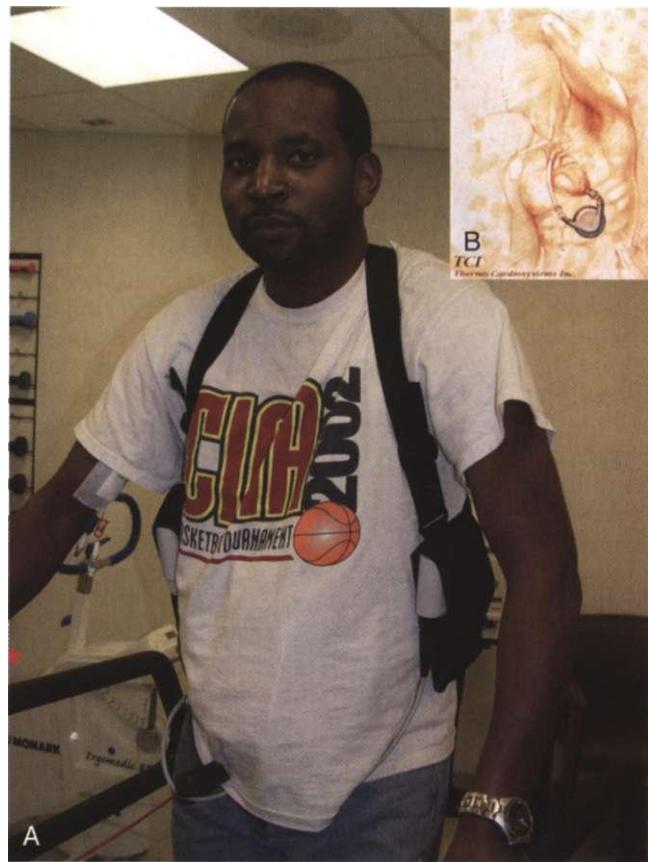


Figure 21-15

A, HeartMate XVE is a vented electrical left VAD that works in parallel with the native heart to support left ventricular function. HeartMate XVE provides sufficient systemic circulation and allows for relatively free mobility so that the person can return home and actively participate in a comprehensive exercise program and other noncontact recreational activities. **B**, Diagram of placement of device. (**A**, Courtesy Chris L. Wells, University of Maryland Medical Center; **B**, Courtesy Thermo Cardiosystems, Inc., Woburn, Mass.)

needs support while their medical or functional status is improved to make them a better transplant candidate, or (3) the team is expecting the patient will have to wait a long time for a donor heart to be found. The use of a VAD as a bridge to transplantation has decreased the mortality rate by almost 50% when compared with medical treatment.²⁷⁸

VADs can also be classified by how the pump circulates blood. Many pumps mimic the function of the heart, meaning the pump has a diastolic or filling time and a systolic phase that ejects the blood forward into arterial circulation. These VADs are considered pulsatile. The rate of the VAD and the amount of blood that is ejected from the pump produces the pump output, which is equivalent to the cardiac output.

The function of the VAD will result in a peripheral pulse and blood pressure. It is important that the clinician remember when verifying the accuracy of the recording from a pulse oximeter that the heart rate on the oximeter should match the pump rate, not the intrinsic

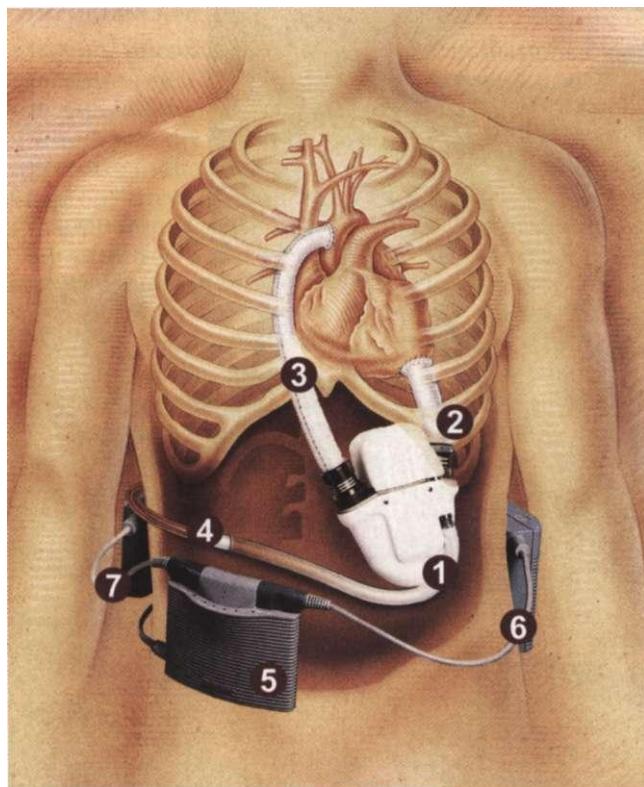


Figure 21-16

Novacor (an implantable electromagnetically driven left VAD that provides systemic circulation. The components of this device include a (1) pump, (2) inflow conduit, (3) outflow conduit, (4) percutaneous lead (driveline), (5) controller, and (6, 7) power packs. Blood circulates from the left ventricle through the inflow conduit into the pump. Upon filling the pump will eject the blood into the aorta via the outflow conduit. (Courtesy WorldHeart, Inc., Oakland, Calif.)

heart rate. Examples of VADs that are pulsatile include the Novacor, HeartMate I, and Thoratec.

Nonpulsatile pumps circulate blood in a continuous manner, meaning there are no systole and diastole phases. The HeartMate II, Jarvik 2000, and VentrAssist are examples of nonpulsatile VADs. How much blood is circulated through the pump will determine if a peripheral pulse can be palpated. The higher the flow through the VAD, the less likely blood will be ejected across the aortic valve, thus creating a peripheral pulse.

If the VAD is pulling larger volumes of blood through it, then there is less blood in the chamber. When the myocardium contracts it does not have enough blood to open the atrial valve and create a peripheral pulse. This makes it very difficult to obtain standard vitals. For these individuals it is important that the clinician properly instruct patients to use a subjective scale like a perceived exertion or dyspnea scale to monitor themselves. Doppler ultrasound may be used to help the clinician obtain vitals.

For right ventricular assistance, blood is typically withdrawn from the right atrium and returned to the main pulmonary artery. For left ventricular assistance, blood is withdrawn from either the left atrium or the apex of the left ventricle. The blood passes through the left VAD and is returned to the ascending or descending aorta.

In general, the VAD has three primary components. There is the pump itself, which is surgically implanted within the body's intracardiac (Jarvik) or intraabdominal wall (Novacor, HeartMate, and VentrAssist). The Thoratec is an example of one VAD that has the pump external to the body.

The second component of VADs is a computer or controller, which is responsible for running the pump. Finally, there must be a power source; the majority of

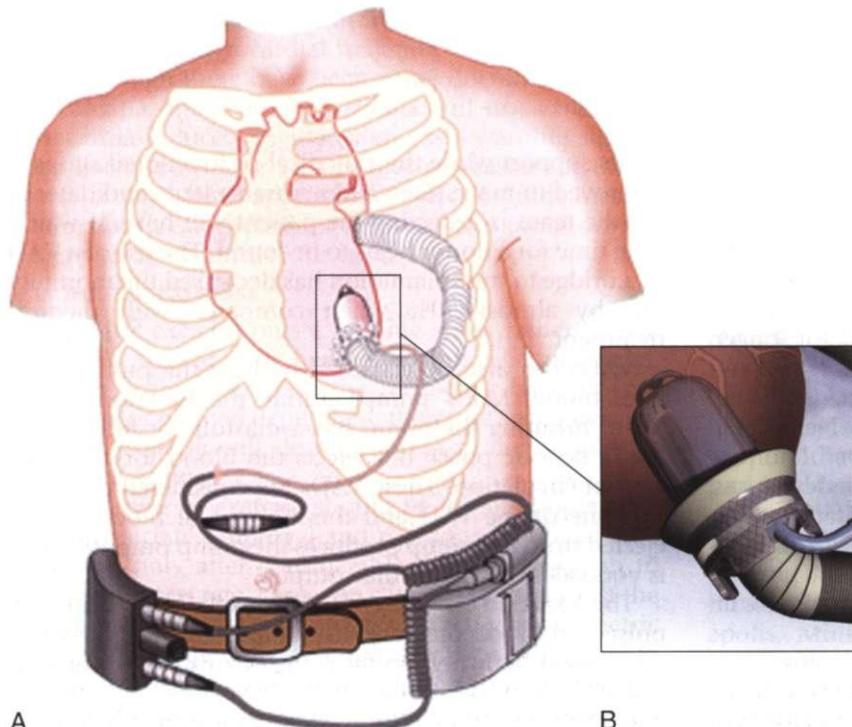


Figure 21-17

Jarvik 2000 is a left VAD that is surgically implanted within the left ventricle and constantly circulates blood by way of a spinning rotor pump. **A**, Full thoracic view. **B**, Inset: Close-up view of the nipple-shaped implant into the anatomic heart. (A, Courtesy Texas Heart Institute, St. Luke's Episcopal Hospital, Houston, Tex., 2000; available at www.texasheartinstitute.org. Used with permission. B, Courtesy Robert Jarvik, MD, used with permission.)

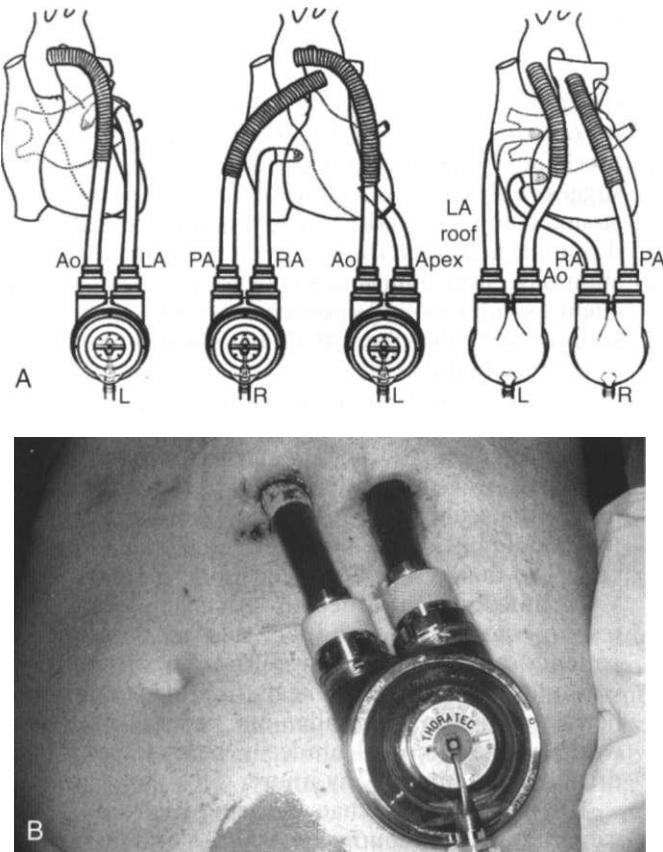


Figure 21-18

A, The Thoratec is a pneumatically driven VAD shown here with various cannulation options. It can support the right, left, or both ventricles. This device is used as a bridge to transplantation or in the case of possible recovery of the native heart function. **B**, Thoratec left VAD. The actual pump is external to the body, which allows this device to be used for people of smaller stature. Another special feature of this device is its ability to support a patient in biventricular or only right ventricular failure. (A, Courtesy Thoratec Laboratories, Pleasanton, Calif. B, Courtesy Chris L. Wells, University of Maryland Medical Center.)

VADs have the ability to run from AC power or a portable battery (see Fig. 21-15). It is important that the therapist have an understanding of how the VADs operate, how to change power sources, and how to attend to any alarms or emergency procedures when working with someone who is being supported by a VAD.

One of the exciting factors when working with anyone on VAD support is the marked improvement in rehabilitation potential. Once the person is stable (often within 24 hours after implantation), the physical therapist should be initiating functional mobility and begin to increase strength, anaerobic, and aerobic capacity.

VADs are capable of increasing pump output and therefore able to increase systemic circulation sufficient enough to allow for an excellent rehabilitation potential. The rehabilitation staff plays a critical role in the management of these individuals by restoring functional mobility, improving exercise tolerance, and preparing the patient for transplantation. The majority of these patients can be discharged home 2 to 3 weeks after implantation

and should be referred to an outpatient clinic and then to a community health club to continue their exercise program.

Besides the use of VADs as a bridge to transplantation, this technology now allows selected people to receive long-term (permanent) support as a substitute for cardiac transplantation. There are several multicenter clinical trials presently underway. The goal is to study the efficacy of VADs as a destination or permanent implantation for the management of end-stage heart failure for people who are not candidates for transplantation (Novacor, HeartMate I, and HeartMate II).^{100,124,131,278} More research will be needed to determine optimal modes of support and predictive factors for those individuals likely to recover.

Indications. VADs are indicated for people with severe heart failure after cardiac surgery, for individuals who have intractable cardiogenic shock after acute myocardial infarction, and in clients who deteriorate while awaiting cardiac transplantation. The use of VADs to salvage individuals with cardiac arrest, severe hemodynamic instability, and multiorgan failure results in a poor outcome at this time; the use of ECMO is a more effective strategy in this group.²³⁸

The general criteria for heart transplantation is the same as for VAD implantation, particularly if the person is being considered for transplantation. The person with pulmonary hypertension may undergo VAD implantation to decrease pressure prior to heart transplantation.

The VAD will decrease the level of pressure in the left atrium by improving forward circulation. This decrease in pressure will lower pressure throughout the pulmonary system if there has not been diffuse or permanent pulmonary endothelial damage.¹²⁴ People considered for VAD as a form of destination therapy may also include older adults, the obese, or people who are seropositive for hepatitis or HIV.

Complications and Prognosis. Device-related infection remains the single most important postoperative complication associated with extended use of VADs, most often arising from the percutaneous driveline exit site. A specialized Dacron (E.I. DuPont de Nemours, Wilmington, Del.) material at the driveline sites promotes skin growth healing around the driveline to minimize infections.

It is critical that all clinicians and the patient make sure the driveline dressing is intact and that the patient is wearing an abdominal binder to decrease stress at the driveline site and prevent disruption of the tissue growth around the line. Researchers are working to develop an antimicrobial driveline that will prevent early infections and facilitate ingrowth of tissue to provide long-term stability and protection against late infection.⁶³ Driveline infections account for 30% of the VAD-associated complications.

Other complications include cerebrovascular accidents, accounting for 10% of deaths. The development of right ventricular failure after left VAD implant is possible. Complications also include bleeding related to prolonged cardiopulmonary bypass, anticoagulopathy, surgical dissection, and liver dysfunction. Pump or mechanical dysfunction or failure is a possibility; there-

fore it is important that the patient and family are trained in emergency procedures. Finally, multisystem organ failure accounts for 27% of VAD-associated deaths.²⁷⁸

SPECIAL IMPLICATIONS FOR THE THERAPIST 21-5

Mechanical Circulatory Support

PREFERRED PRACTICE PATTERNS

4A, 4B: Prevention/Risk Reduction for Skeletal Demineralization; Impaired Posture

5D: Impaired Motor Function and Sensory Integrity Associated with Central Nervous System Disorder (potential complication: cerebrovascular accident); other neuromuscular or musculoskeletal patterns may be present depending on arising complications

6B, 6D: Impaired Aerobic Capacity/Endurance Associated with Deconditioning or Cardiovascular Pump Dysfunction or Failure (orthostatic hypotension common)

7A, 7B: Prevention/Risk Reduction for Integumentary Disorders; Impaired Integumentary Integrity Associated with Superficial Skin Involvement (driveline site)

With an increasing number of centers nationwide routinely implanting these devices along with the increase in clinical trials to use VADs as a destination therapy, and patients allowed to be discharged home, it is likely that therapists in a variety of settings will be exposed to clients with these devices and become involved in the evaluation and treatment progression.

Throughout the rehabilitation process, the therapist must monitor the international normalized ratio (INR) values for risk of bleeding (see the section on INR in Chapter 40), monitor drivelines during transfer training to avoid torsion or pulling, monitor VAD pump rate and pump output at rest and during exercise, observe for volume overload or dehydration (see the section on Fluid and Electrolyte Imbalances in Chapter 5), assess for neurologic and musculoskeletal complications, and observe for any signs of infection (see Box 8-1). In addition, there is a high incidence of orthostatic hypotension in this population, requiring monitoring of vital signs.

Exercise Guidelines

Data are available to support the safety and efficacy of exercise in this population. Some variations to the expected exercise response may occur secondary to VAD implantation, such as pulmonary restrictive patterns that will require assessment and monitoring of pulmonary function. This is especially true in those individuals with exercise-induced dyspnea and those with preexisting pulmonary limitations.¹⁴

Hemodynamic measurements at rest and during exercise are significantly improved in VAD recipients compared with those in ambulatory heart failure awaiting heart transplantation.^{196,278} However, some recipients of the left VAD demonstrate a lower functional capacity than heart transplant recipients. The reason for this appears to be related to the effects of other organ impairment secondary to end-stage con-

gestive heart failure if implantation is delayed, but it typically improves with sufficient VAD support.¹⁵¹

If the mechanical support is implanted before the development of end-stage damage, then exercise capacity remains equal between heart transplantation and mechanical support.¹⁷⁶ On the other hand, it has been suggested that true functional abilities are not demonstrated using the aerobic capacity results from the cardiopulmonary exercise test. Exercise treatment plans should be more appropriately developed based on the client's symptomatic response to exercise, type of VAD support, and the physical therapist's comprehensive evaluation findings.¹⁴⁶

Exercise training should begin in the ICU setting as early as 24 hours postimplantation with the restoration of function, airway clearance techniques, and the progression of ambulation tolerance. The rehabilitation in the acute care setting is very similar to the care that should be delivered for the heart transplant recipients. The therapist will need to understand how the VAD functions in order to understand the VAD response to exercise and be able to monitor the patient's safety during therapy. The therapist needs to work closely with the VAD team to provide a comprehensive program. Typically, the patient should be wearing an abdominal binder in order to secure the driveline and prevent any injury.

The various VADs that are being used in practice vary in how they support the patient's heart and circulation. Some VADs circulate blood by a pulsatile force that mimics the function of the heart, having both a systolic (contraction) and diastolic (filling) phase.

For these VADs, there is no difference in how the vitals signs are monitored. The therapist will be able to monitor pump rate, blood pressure, oxygen saturation, and pump output (see Appendix B). There are other VADs that circulate blood continuously, which means the therapist will not be able to detect a peripheral pulse and may only be able to obtain a blood pressure with the use of Doppler ultrasound.

It is important that the patient learn how to use a subjective scale such as the Borg scale to self-monitor intensity during exertion (see Table 12-13). Using the Borg scale, cardiovascular exercise intensity can be in the "fairly light" to "somewhat hard" range.¹⁴⁶ Usually these clients can progress to independent ambulation on level surfaces by the end of the first week postoperatively, with initiation of treadmill exercise soon after. The majority of clients with a VAD steadily progress through a rehabilitation program, routinely exercising for 20 to 30 minutes at an estimated treadmill workload ranging between 3 and 7 metabolic equivalents.

Termination of exercise may be required in the presence of a narrowing of pulse pressure, abnormal changes in the rate-pressure product, change in mentation, new onset of arrhythmias, any other combination of indicators listed in Table 21-4, or operational changes with the VAD. The therapist must be familiar with emergency procedures specific to each device in case of device failure.

Lung Transplantation

Overview

The first lung transplant was performed in 1963 on a 58-year-old man with bronchogenic carcinoma; he survived for 18 days. Other lung transplants were attempted without success because of lung rejection, anastomotic complications, or infection in the transplant recipients.

Long-term survival was achieved in 1965 with the discovery of chemical immunosuppression, but the real breakthrough came in 1981, when the first successful human heart-lung transplantation was performed for the treatment of pulmonary vascular disease and in 1983 with the first double-lung transplant.^{266,332} The lung is the most difficult organ to preserve its function to allow for harvesting. Upon the brain death of an individual there is a catecholamine storm that occurs, which leads to the disruption of the pulmonary capillary beds. The consequence is pulmonary edema and difficulty with ventilation and oxygenation.

There is also an increased risk to lung injury due to pulmonary contusion if the death of the donor was traumatic, as well as the risk of aspiration and ventilatory-related trauma and pneumonia.²⁶⁶ Less than 15% of cadaveric donors have lungs suitable for harvest.²⁵¹ With the shortage of available donor lungs, approximately 15% of people die while waiting on the transplantation list. The shortage has also led surgeons to accept more marginally functioning organs, perform more single-lung transplantation procedures, and even perform living related lung transplantation procedures in order to attempt to save and improve lives.^{252,266,295}

Indications

At present there are 63 active lung transplantation centers in the United States. Over the past 25 years there has been an expansion in the number of diseases that can be successfully treated by lung transplantation. Currently, chronic obstructive pulmonary disease (usually smoking-related emphysema but also including emphysema due to alpha,-antitrypsin deficiency) is the most common indication, accounting for approximately 45% of all lung transplants.^{68,236}

Other common indications include interstitial pulmonary fibrosis, cystic fibrosis, primary pulmonary hypertension, and Eisenmenger syndrome (pulmonary hypertension secondary to congenital heart disease).

Less frequent indications include sarcoidosis, lymphangiomyomatosis, eosinophilic granuloma, drug-induced and radiation-induced pulmonary fibrosis, and occupational-induced pulmonary diseases, such as silica farmer's lung, that lead to pneumonitis and pulmonary fibrosis. Pulmonary disease arising from an underlying collagen vascular disorder such as scleroderma and lupus can also lead to end-stage lung disease.

Although lung cancer has traditionally represented an absolute contraindication to transplantation, successful transplantation for bronchoalveolar carcinoma has been documented.⁹²

Transplantation Candidates

The timing for referral to a transplantation center is very complicated and depends on many variables. The general practitioner should make an early referral to the center to allow the center to determine the best timing for transplantation evaluation and possible listing.

It is both science and art to determine the best time to list a person for transplantation based on the disease process and its progression, blood type, other medical conditions, and even the activity level of the center. The important thing is to list a potential candidate for transplantation when the data suggest that the person can survive the expected waiting time for transplantation without developing other contraindications to transplantation. Contraindications may include irreversible damage to other organs, certain types of infection, dependency on mechanical ventilation or poor functional capacity,^{110,225} or ambulatory but functional disability. The candidate must be free of clinically significant cardiac, renal, or hepatic impairment.

Until 2005 the allocation of donor lungs was primarily decided by the amount of waiting time a potential candidate had registered with UNOS. In 2005 the Lung Allocation System (LAS) was implemented with the goal to better identify candidates and utilize the very limited resources to achieve the best possible outcomes.

The LAS is based on the previous 6 months of medical information to estimate for each candidate the risk of dying before transplantation, which is then mathematically combined with the probability of survival for the recipient after transplantation. Each candidate is assigned an LAS score; the procurement centers then allocate donor organs based on those LAS scores. The scores can be updated as the candidate's state of health changes (see Box 21-4).^{252,318}

General categories to cluster diseases have been made to include (1) individuals with an obstructive disease (emphysema, and alpha,-antitrypsin deficiency), (2) pulmonary vascular disease (primary pulmonary hypertension and Eisenmenger syndrome), (3) cystic fibrosis and immunodeficiency disorders, (4) pulmonary restrictive disorders (idiopathic and nonidiopathic pulmonary fibrosis), and (5) other.

International disease-specific guidelines for candidate selection have been published (Box 21-12). The average waiting time is decreasing, but it is unclear at this point the effectiveness of the LAS in managing the waiting list; allocating organs and outcomes of lung transplantation depend on blood group, type of procedure, and transplantation location.

The median waiting time is 560 days, with time to transplantation in the 25th percentile of approximately 200 days. Candidates waiting for bilateral lung transplantation procedure typically will wait longer due to the difficulty of finding a donor who has two suitable organs. Individuals who require bilateral lung transplantation typically have cystic fibrosis or Eisenmenger syndrome. These clients tend to be small in stature, which also adds to the waiting time because the donor needs to be smaller than average to be suitable.^{252,316}

Box 21-12**INTERNATIONAL SELECTION CRITERIA FOR LUNG TRANSPLANTATION****General Criteria**

- Must meet criteria listed in Box 21-5

Chronic Obstructive Pulmonary Disease

- $\text{FEV}_1 < 25\%$ of predicted value that does not change or reverse with treatment
- $\text{PaCO}_2 \geq 55 \text{ mm Hg}$ and/or elevated pulmonary artery pressures
- Progressive deterioration (e.g., cor pulmonale, long-term oxygen requirement, significant functional impairments)

Cystic Fibrosis and Other Bronchiectatic Diseases

- $\text{FEV}_1 \leq 30\%$ of predicted value or rapid progressive respiratory deterioration ($\text{FEV}_1 > 30\%$)
- Other indicators of rapidly declining lung function (e.g., increasing numbers of hospitalizations, massive hemoptysis, increasing cachexia)
- Young women with cystic fibrosis who deteriorate rapidly have a poor prognosis (early referral should be considered)

Idiopathic Pulmonary Fibrosis

- Symptomatic, progressive disease (including rest or exercise oxygen desaturation)
- Failure to improve or maintain lung function while being treated with immunosuppressive drug therapy
- Symptomatic or advanced disease as measured by vital capacity $<60\%$ to 70% of predicted value
- Hypoxemia at rest or exercise induced

Primary Pulmonary Hypertension

- Symptomatic, progressive disease (NYHA functional class III or IV with optimal treatment)
- Limited life expectancy (2 to 3 years)
- Hemodynamic parameters
- Cardiac index $<2 \text{ l/min/m}^2$
- Right atrial pressure $>15 \text{ mm Hg}$
- Mean pulmonary artery pressure $>55 \text{ mm Hg}$

Pulmonary Hypertension Secondary to Congenital Heart Disease (Eisenmenger Syndrome)

- Severe progressive symptoms with function at NYHA III or NYHA IV level despite optimal medical management

Modified from Maurer JR, Frost AE, Estenne M: International guidelines for the selection of lung transplant candidates, *J Heart Lung Transplant* 17:703-709, 1998.

The last reported death rate while waiting for a lung transplantation was 134 per 1000 patients, with potential candidates who were over age 65 years and children between 1 and 5 years of age having a higher risk of death while waiting. In 2004, there were 211 deaths per 1000 patients in adults over 65 years and 171 deaths in children per 1000 patients.³¹⁶

Over the years the criteria for listing has become less restrictive at many transplantation centers. As a consequence there has been an increase in people of older ages who have been listed and undergone transplantation. There is an increase in the number of candidates between the ages of 50 and 64 years and in candidates over 65

years of age. Together these two groups account for more than 50% of the candidates.³¹⁶ In general, the following age limits have been recommended: 55 years for candidates for heart-lung transplantation, 60 years for candidates for double-lung transplantation, and 65 years for candidates for single-lung transplantation.²⁰⁶

Many other considerations are used in the determination of a lung transplantation candidate because of the potential complications associated with these factors (see Box 21-5). Some of these variables include the presence of severe osteoporosis, the degree of systemic and pulmonary hypertension, diabetes mellitus, and coronary artery disease that may worsen after transplantation; mechanical ventilation at the time of transplantation (higher mortality rate); underlying collagen vascular disease; presence of antibiotic-resistant infections, especially *Burkholderia cepacia* (a multiresistant bacterial respiratory infection associated with severe and often lethal postoperative infections); and previous thoracic surgery.¹³

Transplantation Procedure

The four major surgical approaches to lung transplantation are single-lung transplantation, bilateral sequential transplantation, heart-lung transplantation, and transplantation of lobes from living donors. Single-lung transplantation has been the most commonly used procedure because of the ease with which it can be done and the fact that one donor can be used for two candidates.

Single-lung transplantation requires a posterolateral thoracotomy, whereas double-lung transplantations are typically done through bilateral anterior thoracotomies and a horizontal disruption of the sternum, referred to as a "clam shell." In this latter procedure, the rib cage and sternum are lifted anteriorly and superiorly as you would lift the hood of your car. This procedure allows good visibility of the mediastinum. The heart-lung procedure is still generally performed through a mediasternotomy.

In general, donor lungs should be the same size or just slightly larger than the recipient so that the donor lobes fill each hemithorax, avoiding persistent pleural space problems in the recipient. However, donor lungs must have a lung volume similar to or less than that of the intended recipient; larger lungs in single-lung transplantation can be placed on the left side, where the diaphragm has the potential to descend because of the absence of the liver under the left hemidiaphragm. In living related donations, a lobe (generally the right or left lower lobe) is removed from each of the two donors and is used to replace the lungs of the recipient.

There is an increased risk of a reperfusion injury to the donor lung. However, for candidates with pulmonary vascular disease, both single-lung transplantation and double-lung transplantation can result in immediate and sustained normalization of pulmonary vascular resistance and pulmonary arterial pressures. This good result is possible if the proper medical care, including accurate size of the donor organ and the use of prostaglandin medications, is provided in the pretransplant, perioperative, and posttransplant periods.¹⁰³ There is an immediate increase in cardiac output and gradual remodeling of the right ventricle with a decrease in ventricular wall thickness.

Complications

Postoperative complications of primary lung transplantation include infection; dysfunction of the bronchial and/or vascular anastomoses, including bronchial stricture or malacia, stenosis, or occlusion of the venous anastomoses; and acute or chronic rejection.

Graft Failure. Within the first 30 days the primary cause of death is from primary graft failure. This is primarily attributed to an ischemic reperfusion injury sustained in the perioperative or acute postoperative period and occurs in some degree in 30% of all lung transplant recipients.

Graft failure due to ischemic reperfusion injury accounts for 30% of the deaths within the first 30 days and another 30% in the next 60 days. Ischemic reperfusion injury may lead to acute lung injury, previously referred to as adult respiratory distress syndrome associated with an aggressive inflammatory response leading to cell injury, and loss of endothelial barrier function.²⁵²

Other causes of death within the first 30 days include non-CMV infections, which account for 23% of the deaths and other complications (20%) such as coagulopathy, disruption of one of the anastomoses, and ventilatory-induced injury.^{295,316} In the case of acute graft dysfunction, ventilation needs may exceed the parameters of standard mechanical ventilation and ECMO may be required, in which case gas exchange takes place entirely, or in part, outside the body (Fig. 21-19). See further discussion in the section on Future Trends later in the chapter.

The leading causes of death for lung transplant recipients vary based upon the posttransplant time. The leading cause of death within the first year is from non-CMV infections (39%) followed by graft failure and other complications such as bronchial anastomosis dysfunction. After 3 years the primary cause of death is related to chronic rejection, which is referred to as bronchiolitis obliterans, and there is an increasing rise in death associated with renal failure and cancer and complications of diabetes.^{70,295,331}

Bone Density Loss. Glucocorticoid-induced changes in bone density are a significant medical complication after lung transplantation. In fact, unlike other transplant recipients who develop osteoporosis after surgery from antirejection drugs, lung recipients are more at risk for osteopenia or osteoporosis as a result of pretransplant exposure due to several factors, including decreased muscle mass and weight-bearing activities.^{70,295,331}

Individuals with lung disease are commonly exposed to corticosteroids (acute, high-dosage, or long-term use) for their positive antiinflammatory effects. Besides the pretransplant exposure to corticosteroids, lung transplant candidates commonly suffer from poor absorption of nutrients associated with the underlying disease process (e.g., cystic fibrosis, collagen vascular diseases). This is especially true for individuals with cystic fibrosis, who often have malabsorption deficits and enzyme deficits to utilize vitamin D that further increase their risk.

Immunosuppressive medications such as cyclosporine, mycophenolate mofetil, and azathioprine may be used in the pretransplant period for the management of

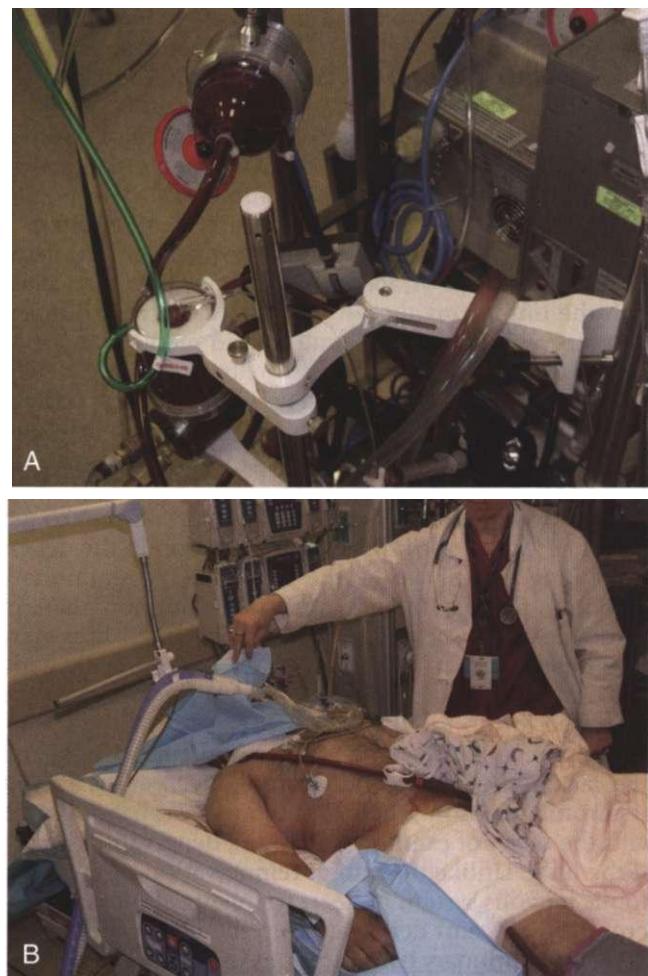


Figure 21-19

Extracorporeal Membrane Oxygenation (ECMO). **A**, ECMO is used to support the cardiopulmonary system by controlling gas exchange and assisting the heart in blood circulation. With ECMO, venous blood is circulated through a CO₂ scrubber and membrane oxygenator (white canister) and returned to the body via a centrifuge pump (red and silver machine) as oxygenated blood with a desired PaCO₂ and PaO₂. **B**, Depending on how the machine is cannulated to the patient, ECMO can assist or control cardiopulmonary function. The cannulation sites in this individual are the femoral vein and artery. In more critically ill patients the cannulas can be inserted in the inferior vena cava or right atrium and the aorta, primarily bypassing cardiopulmonary function. Work is currently being done to develop an ECMO system that would allow the patient to be mobilized out of bed and allow more aggressive rehabilitation to prevent adverse effects of immobility. (Photos courtesy Chris L. Wells, University of Maryland Medical System.)

autoimmune diseases such as scleroderma and lupus, which further results in osteopenia and osteoporosis. The incidence of osteoporosis of the vertebral spine is 29% in pretransplant lung candidates, and bone loss continues posttransplant, with up to 20% of recipients having a significant progression of their disease.^{37,193}

Lung transplant recipients are more likely to be exposed to higher immunosuppressive levels and longer exposure to corticosteroids than other organ transplant recipients due to the highly vascular and immunogenic nature of the lung, which further compromises the health of

bone.^{331,332} (See the section on Side Effects of Immunosuppressants in this chapter, and see also Chapter 5.)

Gastrointestinal Disorders. Gastrointestinal problems are a considerable source of morbidity for lung transplant recipients. The most common major complication is diverticulitis, requiring colectomy. Malignancy occurs slightly less often; minor problems such as polyps and benign anorectal disease have also been reported.¹¹³

Lung transplant recipients also acquire the problems associated with poor absorption of nutrients associated with the underlying disease process (e.g., cystic fibrosis, collagen vascular diseases) and steroid medications used to treat their lung conditions before transplantation. This is especially true for individuals with diseases such as cystic fibrosis, who often have malabsorption deficits and enzyme deficits to utilize vitamin D that further increase their risk.

Pulmonary Problems. The absence of the cough reflex and diminished mucociliary function in the denervated lung contribute to the frequency of pulmonary infection (at least three times more common than in heart transplant recipients). The transplanted lung may have deficiencies in lymphatic drainage, especially early after transplantation, and mucociliary function may be depressed for up to 16 weeks.

Recipients frequently develop chronic bronchitis and may lack bronchus-associated lymphatic tissue as a result of chronic rejection. There is a delay in bronchodilation with the onset of exertion due to the denervation nature of the lung. Unlike the partial reinnervation of the autonomic nervous system in heart recipients, there is a long-term persistence of denervation in the donor lung.²⁹⁵

Other pulmonary complications include trauma to the phrenic nerve, anastomosis dysfunction, and native lung hyperinflation. Although phrenic neuropathy is an infrequent complication of lung transplantation, the therapist may see evidence of it with subsequent diaphragmatic dysfunction. Phrenic neuropathy as a complication of surgery is possibly caused by phrenic nerve injury.

Clinical evidence of phrenic nerve damage may include atelectasis, pneumonia, elevated hemidiaphragm, and prolonged ventilatory support. Narrowing of the bronchus can occur from the formation of granulation tissue or fibrosis or narrowing because of malacia. A stent can be placed within the airway to stabilize the lumen and allow for sufficient air flow.⁶

In individuals with an underlying obstructive disease (most commonly emphysema) who undergo a single-lung transplant, either acutely or chronically, the native lung can develop further hyperinflation due to increased lung compliance and the presence of bullous disease. The lung can displace the mediastinum away from the native lung; lead to the decrease in pulmonary function, dyspnea, tachycardia, and flattening of the diaphragm; and, if severe, can alter the flow of blood flow through the cardiac system.⁶

Rejection. The lung transplant recipient needs to be continuously monitored for rejection. Hyperacute rejection is predominantly an antibody-mediated response that results immediately after revascularization and leads to a massive immune response, thrombus formation, and destruction to the donor lung. The patients are critically

ill and may require ECMO. There is a high mortality rate for individuals who suffer from hyperacute rejection.^{230,332}

Acute rejection is generally a T cell-mediated response. Class 1 HLA antigens located in all nucleated cells are recognized by CD8 recipient cells that mediate the immune response, whereas class 2 HLA antigens are found in endothelial cells that activate CD4 T lymphocytes. Both T cell-mediated responses lead to the activation and proliferation of the recipient's immune response.²³⁰

Some people in acute rejection will be asymptomatic; but when a person in rejection is symptomatic, clinical manifestations may present as dyspnea, fatigue, fever and chills, oxygen desaturation, decreased exercise tolerance, and changes in x-ray findings (see Table 21-3). The recipient may suffer significant respiratory distress or even failure, requiring mechanical ventilator support. Recipients frequently use a home spirometer to check for expiratory indices (e.g., forced expiratory volume [FEV₁]), and monitor exercise tolerance, which will show a decline as a consequence of acute rejection.

Chronic rejection is referred to as bronchiolitis obliterans (BO), which accounts for 30% of deaths in the first-year posttransplant adults and is the leading cause of death in children within the first year.³³¹ BO is the fibrotic occlusion of small airways due to adverse effects of rejection on the donor lung and is diagnosed by biopsy.

Bronchiolitis Obliterans Syndrome (BOS) is a cluster of signs and symptoms of chronic rejection but has not been diagnosed as having cellular changes; BO cannot be confirmed in up to 50% of recipients. BOS is defined as a decrease in FEV₁ greater than 20%, which cannot be attributed to acute rejection or infection.²⁵²⁻²⁵⁴ BO or BOS is associated with the following risk factors: frequent and severe episodes of acute rejection, lymphatic bronchitis, viral infection, gastroesophageal reflux disease, CMV, and prolonged ischemic times.³³¹

Infection. There is an increase incidence of infections in lung transplant recipients because of increased levels of immunosuppressive medication, decrease in ciliary function, insufficient mucus clearance and cough, poor nutritional status, and the fact that the lung is exposed to environmental factors. Signs and symptoms of infection may be very difficult to distinguish from acute rejection (fever, tachycardia, tachypnea, fatigue, malaise, decrease in exercise tolerance, oxygen desaturation, and respiratory failure) except there is an increase in sputum production with a productive cough.

Lung transplant recipients are at risk for other complications, as previously discussed in other transplantation sections of this chapter. These complications include cancer, which accounts for up to 15% of recipient deaths. Renal dysfunction is present in almost 40% of lung transplant recipients. There is a high prevalence of cardiac risk factors as well, with 45% of recipients having been diagnosed with hyperlipidemia; 28% develop diabetes, and almost 90% are diagnosed with systemic hypertension.^{252,295,316}

Prognosis

Survival rates for lung transplantation continue to improve as surgical techniques and postoperative care

improve despite the fact that the recipients are older and there has been an expansion of the medical criteria for donor lungs. The 1-, 3-, and 5-year survival rates for single and bilateral transplants are 83%, 62%, and 46.5%, respectively. Lower survival rates are found for retransplantation, with a 26.6% survival at 5 years.³²⁰

There are few heart-lung transplants performed annually. The complexity of candidate medical status, the technical surgical issues, and the management of both heart and pulmonary function lead to a decrease in survival when compared with isolated lung transplantation. The 1-, 3-, and 4-year survival rates are approximately 67%, 48.5%, and 38.5%, respectively.³²⁰

Future Trends

More than with any other organ transplantation, biopsychosocial considerations impact lung disease. The rise in numbers of adolescents and young adults who are smoking will contribute to the development of lung disease in future years (see the section on Substance Abuse-Tobacco in Chapter 2). Prevention programs must be a major part of our effort to reduce lung disease and the need for lung transplantation.

Transplantation of lobes from living donors is an acceptable procedure although still somewhat controversial, primarily with selected cases of cystic fibrosis, although the indications will be expanded over time. Two lobes obtained from live donors can adequately support an adult with cystic fibrosis.²⁷⁵ Clinical risks to the living donor are minimal, with very low mortality rates.

Researchers are also working toward development of a thoracic artificial lung (A-lung, sometimes referred to as an intravenous membrane oxygenator) (Fig. 21-20). This new device is designed to treat respiratory insufficiency, acting as a temporary assist device in acute cases or as a bridge to transplantation in chronic cases.^{35,96}

The concept of the A-lung comes from the function of ECMO, but the focus is to make the intravenous membrane oxygenator more portable and durable so that the individual can be supported for longer periods of time and become ambulatory. Efforts to develop the A-lung remain under investigation and have not been approved for clinical use in the United States. Anyone needing pulmonary support of this type still uses ECMO (see Fig. 21-19).

Others are working on similar devices, including providing partial or complete respiratory support depending on the surgical site of the cannulas for blood circulation. These devices are still in the experimental stages of development at this time.¹⁸⁹

Other research to develop ambulatory ECMO as an emergent rescue intervention for pulmonary hypertension and the use of membrane oxygenation as a temporary bridge is undergoing clinical trial. The latter is to support individuals for a brief period as a temporary bridge to lung transplantation in cases of respiratory insufficiency, particularly with pulmonary hypertension. A simpler, safer, and cost-effective alternative to ECMO would allow earlier intervention.

The potential benefits in utilizing either an artificial lung device or ambulatory ECMO device are significant and include a more effective way of oxygenating the indi-

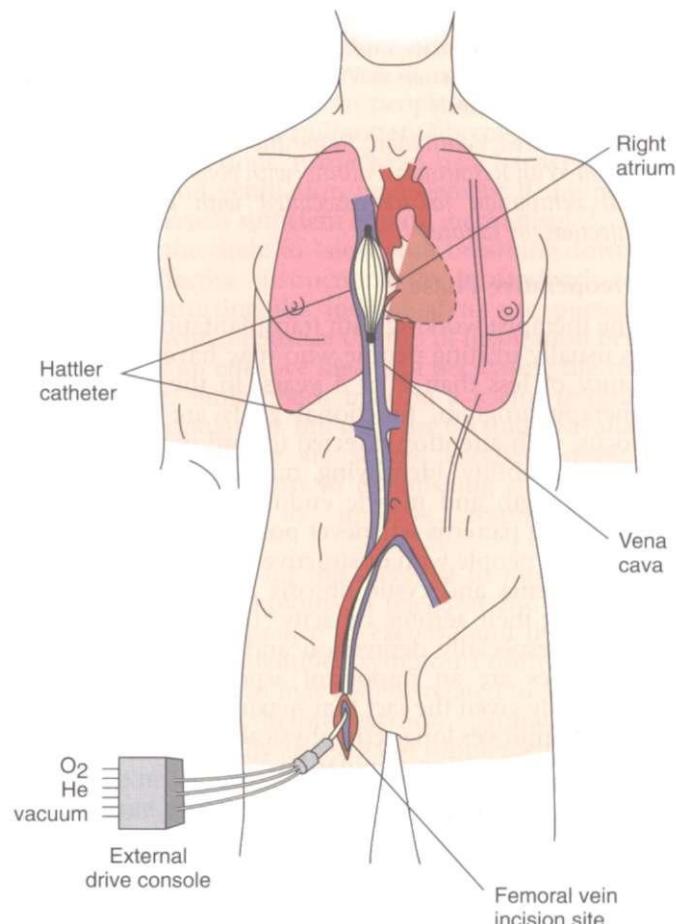


Figure 21-20

Hattler catheter (artificial lung or intravenous membrane oxygenator). The catheter is made up of hollow fiber membranes, which carry oxygen through the fibers to saturate the blood while carbon dioxide is removed from the blood through other fibers. There is a pulsating central balloon in the center of the catheter, which helps mix the blood with the fibers and increase gas exchange. The empty rectangle represents the external device that connects to the catheter and to the individual controls of the catheter. (Courtesy Brack Hattler and W.J. Federspiel, University of Pittsburgh Medical Center, 2000.)

vidual while preventing the adverse effects of immobility. It may even provide a means for long-term "respiratory dialysis."¹⁹⁴ Xenotransplantation is also under intense scrutiny, with some encouraging experimental results (see section on Xenotransplantation in this chapter).

SPECIAL IMPLICATIONS FOR THE THERAPIST

21-6

Lung Transplantation

PREFERRED PRACTICE PATTERNS

4C: Impaired Muscle Performance

4G: Impaired Joint Mobility, Muscle Performance, and Range of Motion Associated with Fracture (secondary to medications)

6B: Impaired Aerobic Capacity/Endurance Associated with Deconditioning

Continued.

6C, 6E: Impaired Ventilation, Respiration/Gas Exchange, and Aerobic Capacity/Endurance Associated with Airway Clearance Dysfunction or Ventilatory Pump Dysfunction or Failure, respectively

6F: Impaired Ventilation, Respiration/Gas Exchange Associated With Respiratory Failure (with potential for mechanical ventilation failure associated with lung rejection, infection, or failure)

Preoperative Phase

The therapist working with transplantation candidates is usually treating people who may have a life expectancy of less than 2 or 3 years. In the preoperative therapy program, functional goals are the primary focus, with attention directed toward increasing functional mobility; identifying, maintaining, or improving strength and muscle endurance; and improving breathing patterns whenever possible.

Many people with obstructive lung diseases such as emphysema and cystic fibrosis are typically able to improve their aerobic capacity. The psychosocial elements, especially depression and anxiety, that affect outcomes are an important aspect of intervention, especially given the fact that maximizing psychosocial status improves long-term physical health outcomes in the transplantation population.⁷⁶

Acute Care Phase

Following the initial surgery, the ICU plan will focus on supporting respiratory function and initiating airway clearance techniques to minimize the risk of infections, stabilize hemodynamics, and mobilize out of bed to begin functional training. During this acute phase the patient will be monitored closely for an ischemic and reperfusion injury and rejection.

It is important that the therapist monitor vital signs, including oxygen saturation and breathing patterns. A few centers place these patients on reverse isolation, but for most the medical staff will follow standard precautions. Therapy should be initiated on postoperative day 1 and may range from positioning for skin care and pulmonary management to beginning functional mobility.

Positioning affects blood flow to lung regions in much the same way that it affects ventilation. Blood flow is greatest in dependent areas of the lung. Unfortunately, these areas may not have the greatest number of ventilated alveoli so that ventilation/perfusion mismatching results.

Posttransplant pulmonary blood flow and ventilation are variable and may be affected by the function of the graft, function of the native lung, presence of pulmonary hypertension, a change in cardiac output, or diaphragmatic function. For the patient who is having difficulty with ventilation and perfusion, the therapist will begin to assess oxygenation and breathing patterns to determine the optimal position to maximize respiratory function.

POSITIONING

In some centers it has been advised that single-lung transplant clients should be placed in the side-lying

position with the transplanted side up and the native lung down. This was thought to help to decrease the edema and compression in the new lung and promote drainage as well as decrease mediastinal shift toward the operative side, thus promoting optimal inflation.

In contrast, it has been advised that during an episode of acute rejection, when perfusion to the transplanted lung is severely diminished, the transplanted lung was to be positioned down with the native lung up to increase perfusion. Research in this area is needed; one study has shown that positioning needs to be evaluated on an individual basis and may change over the course of the postoperative period.¹⁰⁵

Positioning may depend on the severity of an ischemic reperfusion injury and its state of healing, which can usually be determined within the first 10 days postoperatively. If the injury is severe, it may progress to diffuse alveolar disease. Other factors that may affect positioning tolerance include rejection, infection, cardiac output, renal function, and skin integrity.

The simple use of towel rolls or pillows can aid in optimal positioning of the chest and spine in any of the intervention or resting postures to help decrease the work of breathing. Careful attention must be given to the positioning of the upper extremity to aid in or discourage the recruitment of accessory muscles in conjunction with surgical incision precautions (see Box 12-3).

The client is usually weaned from a ventilator within 24 to 48 hours, but some people may remain on a ventilator longer. Supplemental oxygen is usually no longer necessary by the time of hospital discharge. Client education, including various airway clearance techniques, handwashing skills, strength training, and breathing exercises are initiated early in the recipient's recovery.

AIRWAY CLEARANCE AND BREATHING TECHNIQUES

The therapist will need to assess respiratory function along with a complete evaluation to determine the best airway clearance technique (ACT) and ventilatory strategies to maximize ventilation and oxygenation. Traditional chest physical therapy can be completed early in the postoperative period if the person is hemodynamically stable.

The therapist must consider the risk and benefits of completing percussion and vibration in Trendelenburg positions. Current research suggests there is an increase in silent aspiration due to gastroesophageal reflux that worsens pulmonary function.^{48,49}

If the therapist does position the person in a Trendelenburg position, the therapist should not complete the treatment right after feeding. The postpyloric position of the feeding tube should be documented and feeding should be stopped at least 30 minutes before treatment. The therapist should also coordinate ACT with pain medications and ventilation weaning protocols.

Before and after every manual ACT, the therapist must inspect the chest tube sites to rule out air leak

Box 21-13**EFFECTS OF LUNG DENERVATION**

- Decreased tidal volume
- Decreased lung compliance
- Decreased chest wall compliance
- Delay in bronchodilation
- Impairment of mucociliary blanket
- No cough reflex
- Decreased breath holding
- Loss of Hering-Breuer reflex*
- Increased work of breathing
- Increased dyspnea
- Exercise
 - Decreased tidal volume
 - Decreased minute ventilation
 - Increased respiratory rate

*Increased volume on inspiration will reflexively decrease respiratory rate with a period of apnea (cessation of breathing).

and subcutaneous emphysema. Care should be taken not to apply any ACT directly over the insertion site. The recipients will have a decrease in coughing and efficient breathing because the lung is denervated (Box 21-13) and as a result of pain, anxiety, and possibly a decrease in mental alertness.

Conditioned breathlessness is a term that applies to the lung transplant recipient. These clients often need to relearn how to normalize the breathing pattern and to understand that the feeling of breathlessness does not necessarily indicate a lack of oxygen, infection, or rejection, but is instead a function of anxiety and muscle fatigue. Exertional dyspnea and tachypnea are usually seen for several weeks postoperatively.

There are several techniques that can be utilized to improve the recipient's breathing pattern. Diaphragmatic breathing should be facilitated if the phrenic nerve is intact. Positioning in slight trunk and hip flexion will relax the abdominal wall to decrease the work of the diaphragm.

The therapist will need to examine the movement of the diaphragm in various positions (supine, side-lying, prone, sitting) to determine the best position for training. Segmental breathing exercises can be used to facilitate diaphragmatic breathing and chest wall expansion. Inspiratory hold, pursed-lipped breathing, and phonation exercises may be effective tools to improve breath control.

Soft tissue and joint mobilization to the thoracic spine, rib cage, and abdominal wall can be effective manual techniques to improve chest wall mobility and therefore decrease the work of breathing. Once the surgical incision is healed, scar management should begin in order to avoid soft tissue restriction, decreased rib mobility, and chronic pain.

Finally, upper extremity muscle endurance exercises should focus on improving accessory respiratory function. Strengthening of scapula and thoracic spine musculature should be addressed to further improve the breathing pattern and decrease dyspnea.^{19,20}

Anxiety control in clients with severe hypoxemia can help decrease respiratory rate and improve the breathing pattern. However, it is very difficult to decrease respiratory rate in people with lung disease, especially interstitial pulmonary fibrosis, even during nonanxious periods. Anxiety can be a barrier to rehabilitation and ventilation management if the person does not have a sufficient coping mechanism.⁷⁷

Telling the client to "slow your breathing down" is not an effective instructional or biofeedback technique. Instructing the individual to use pursed-lip breathing with a pause at the top of inspiration before exhaling is an effective means of decreasing the respiratory rate. Biofeedback may be a useful technique with this population, but there are no studies available in this area. There are several excellent resources to guide the therapist in establishing specific therapeutic exercises to improve respiration and phonation.^{101,132,203,204}

It is important for the therapist to monitor vitals and signs and symptoms of rejection and infections. A decrease in tolerance to exercise and desaturation may be the first identified symptoms during exercise. Subtle desaturation may also be related to insufficient warmup periods before exertion. Saturation levels should be normally above 93%; supplemental oxygen may be needed when saturation levels are at or below 90% (see Table 21-4).

It may be beneficial to use supplemental oxygen during therapy to maximize the rehabilitation potential. Any changes in exercise tolerance and vitals should be reported to the transplantation center for further investigation.

Once basic functional mobility is restored, therapy should focus on progressing aerobic exercise, muscular strength, and endurance tolerance. If pulmonary function is insufficient for extubation, functional mobility training and strengthening should progress as appropriate with proper mechanical ventilation support, including supplemental oxygen to help the person progress and contribute to the weaning process.

Outpatient Phase

Client education regarding the importance of consistently following an at-home or community-based program to increase and maintain metabolic equivalent level (multiples of resting oxygen consumption) with exercise is essential.

It is recommended that the recipient be referred to outpatient physical therapy for further strength and functional training, with the goal of improving exercise capacity so that the person can participate easily in community-based activities without fatigue. The recipient should be able to self-monitor and progress through the exercise program independently.

A traditional pulmonary rehabilitation program is an effective therapy for recipients whose primary limitation is aerobic tolerance and who would benefit from extensive client education and support. The majority of people should participate in a walking program to help minimize weight gain, muscle

Continued.

atrophy, osteoporosis, and edema (effect of cyclosporine on kidneys). The therapist should verify on a weekly basis that the recipient is compliant with self-monitoring of blood pressure and spirometry volumes and report any changes to the physician's office.

The peak effect of transplantation on lung function is typically within 3 to 6 months, at which point the limiting effects of surgically related factors (e.g., post-operative pain, altered chest wall mechanics, respiratory muscle dysfunction, acute lung injury) have dissipated. After double-lung replacement, normal pulmonary function is usually achieved. Lung function improves but may not reach predicted levels.¹³

Exercise

Before lung transplantation, candidates are characterized by very low exercise capacity ($V_{O_2\text{max}}$ 14 ml/kg/min) because of the restricted oxygen uptake caused by reduced ventilatory capacity, ventilation/perfusion mismatching, or decreased diffusion capacity and/or blood shunting.¹⁹⁸

After transplantation, overall pulmonary function improves and exercise capacity increases because the lungs can now perform maximal oxygen uptake and maintain oxygen saturation levels over 90% during submaximal exercise (see also the section on Exercise, Activity, Sports, and Organ Transplantation in this chapter). An aerobic endurance training program improves submaximal and peak exercise performance significantly in lung transplant recipients.^{292,293}

By the end of the first year after transplantation, approximately 80% of recipients report no limitations in activity; exercise is not limited by ventilation despite a decrease in tidal volume and increased respiratory rate with exercise.²⁶² However, the recipients reach only 40% to 60% predicted V_{O_2} capacity.^{6,118,139} The therapist should continue to follow the guidelines outlined in Table 21-4.

Despite these improvements, cardiopulmonary exercise testing has consistently shown that $V_{O_2\text{max}}$ in recipients of single- and double-lung transplants is still lower than sedentary, healthy, matched control subjects.^{108,334} Maximal oxygen consumption is depressed despite the absence of clinically significant cardiac or ventilatory limitations on exercise. There is evidence that the continued decrease in exercise capacity is related to deficits in oxygen extraction, abnormal microcirculation oxygen delivery, anemia, and alterations in muscle fiber type and oxidative enzymes.^{6,118,181,262}

A number of studies have shown that lower limb skeletal muscle dysfunction may be a major factor in exercise limitation. Clients report lower extremity fatigue rather than dyspnea as the main reason for exercise intolerance. There may be an intrinsic abnormality of the skeletal muscle in recipients of transplants. An in-depth summary of exercise limitations in this population is available.²⁰⁵

Pancreas Transplantation

Overview

Pancreas transplantation has become an accepted therapeutic approach to treat type 1 diabetes, which is caused by the autoimmune destruction of pancreatic islet beta-cells, thereby successfully restoring normoglycemia. Pancreas transplantation is performed only for people with type 1 diabetes mellitus since a new organ will not improve the body's inability to use insulin, as is the case with type 2 diabetes.

Although pancreas transplantation represents a physiologic approach to reverse diabetes mellitus, a new technique of pancreas islet beta-cell transplantation is now in the experimental phase. Transplanting insulin-secreting cells is a low-invasive procedure with the possibility of modulating graft immune response before transplantation, allowing reduced or minimized immunosuppressive medications.³³⁰

In June 2000 the *New England Journal of Medicine* pre-released the findings of a report (the Edmonton protocol) from researchers injecting pancreas cells near the liver in eight people with type 1 diabetes. The cells took up residence in the liver and began producing insulin.²⁷³

Since that time continued advancement has occurred through extensive collaboration between key centers.¹⁸⁰ For example, results at nine international sites report islet transplantation from deceased donors within 2 hours after purification has been used to restore long-term endogenous insulin production and glycemic stability in a small number of individuals with type 1 diabetes. Insulin independence has not been sustainable; it is often required again at 2 years.²⁷⁴

There are still limitations with this approach, but newer pharmacotherapies and interventions designed to promote islet survival, prevent apoptosis, promote islet growth, and prevent immunologic injury are approaching clinical trial status.²⁰⁹

Indications

Unlike heart, lung, or liver transplants, pancreas transplantations are not an immediately life-saving procedure. Recipients have to be carefully selected in order to reduce morbidity and mortality; investigation of myocardial and cerebral vascularity is essential.

Even with these guidelines, pancreas transplantation has become a routine treatment for type 1 diabetes with uremia or for those who previously received a kidney transplant. Pancreas transplantation at the same time as a renal transplant is considered more often now, especially if the diabetes has been difficult to control.²⁶⁷

Although the recipient must remain on lifelong immunosuppressive medications, 80% to 90% 1-year survival rates are considered very acceptable given the alternatives of insulin therapy, dietary restrictions, hypoglycemic and hyperglycemic episodes, dialysis, and potential long-term complications associated with diabetes mellitus.⁶⁵ Research shows that pancreas transplants can provide excellent glucose control in recipients with type 2 diabetes.²²⁴

Diabetic nephropathy is the leading cause of kidney failure in people with type 1 diabetes. Successful pancreas

transplantation leads to normal glycemic control in people with type 1 diabetes, but historically this type of transplantation has been limited to people with both kidney failure and diabetes. Pancreas transplantation does not reverse the advanced complications (e.g., diabetic retinopathy, vascular sclerosis) present with long-term diabetes. However, the effect of pancreas transplantation on reversing neuropathy (i.e., improved nerve action and potential amplitudes) is possible.⁹

Despite the difficulty of this surgical procedure and the many potential complications, pancreas transplantation before the development and progression of diabetic nephropathy is being suggested for this population group.^{140,290} However, this is a controversial subject since others feel that, in the absence of end-stage renal failure, there is no justification for pancreas transplants alone except where diabetes itself poses a greater risk to life than the transplantation procedure.

Individuals with diabetes and renal involvement and individuals with unstable diabetes may be helped with an islet or pancreas transplant, but this approach is still considered experimental. Such transplantation may speed up the need for a kidney replacement. For individuals with well-controlled diabetes and intact function, pancreas or islet transplantation may not be advised given the risks of immunosuppression following transplantation.²⁶⁷

Combined pancreas-kidney transplantation is an accepted treatment for carefully selected candidates with type 1 diabetes and ESRD and in a small group of individuals with uncontrolled severe metabolic problems.²⁷²

Transplant Candidates

Many centers consider pancreas transplantation contraindicated in people with cardiovascular disease, especially atherosclerotic vascular disease and congestive heart failure, because of the poor outcome after pancreas transplantation when either of these risk factors is present. Some centers may consider transplantation in cases of atherosclerotic vascular disease if coronary lesions are corrected before transplantation. Other risk factors include age older than 45 years, obesity, and hepatitis C.¹⁹⁷

Transplantation Procedure

The donor pancreas is most often placed extraperitoneally on the right side using the recipient's (native) vessels. It is necessary to drain the pancreatic exocrine secretions by channeling them to the urinary bladder or into the stomach. This may be accomplished with a variety of surgical techniques.

In the case of pancreas islet cell transplantation, cells removed from a cadaver are injected into the blood vessel leading to the liver (portal vein). Since development of these procedures is in its infancy, they presently require the cells from two pancreases, matched for blood type, to produce an apparent cure. Better methods for extracting cells from the donated pancreas or a way to grow the cells in the laboratory are being investigated.

Complications

Surgical complications remain the primary source of morbidity after pancreas transplantation (especially when

combined with a simultaneous kidney transplantation), affecting approximately 35% of studied cases.²⁵⁹ This may change with continued advances in surgical techniques, but data are limited at this time. Specific complications include graft vascular thrombosis, pancreatic hemorrhage, intraabdominal bleeding or infection, allograft failure, and urologic problems associated with the bladder drainage surgical technique.

Other nonsurgical complications may include post-transplant pancreatitis possibly secondary to ischemia reperfusion microvascular injury and the more typical transplantation complications associated with other solid organs, such as infection and side effects of prolonged immunosuppression.

Complications of the pancreatic islet cell transplantation are minimal, but long-term safety and effectiveness of this technique remain to be proven. The recipients must take a combination of three immunosuppressive medications to prevent the body from rejecting the transplanted cells. The increased risk of cancer, infection, and other long-term side effects associated with these medications has been discussed.

Prognosis

Over the past 20 years there has been a progressive improvement in outcomes after pancreas transplant, simultaneous pancreas-kidney, and pancreas after kidney transplantation.¹²¹ Vascular disease remains the major cause of both morbidity and mortality after transplantation in recipients who have diabetes and is correlated with the degree of vascular disease before transplantation. Graft and recipient survival rates in diabetic recipients are higher when the recipient receives simultaneous pancreas-kidney transplantation. These survival rates are even higher when the kidney donor is a living related donor.²⁵⁸

Compared with other abdominal transplants, pancreas transplants have had the highest incidence of surgical complications. This trend may be reversing owing to identification of donor and candidate risk factors, better prophylaxis regimens, refinements in surgical technique, and improved immunosuppressive regimens.¹⁶⁸ Steroid withdrawal is possible in up to 70% of pancreas transplant recipients as long as the person is maintained on some form of immunosuppression (usually tacrolimus [FK506]).^{144,157}

Even with surgical complications, pancreas transplant recipients' survival rates are 94% at 1 year and 80% at 3 years.¹²¹ Data on survival rates following islet transplantation are limited given the recent development of this technique and the scarcity of donor islet cells.

Of those people who have received autotransplants worldwide following total or subtotal pancreatectomy, insulin independence has been achieved in 40%. Islet allotransplantations have demonstrated improved metabolic control in more than 50% of cases and insulin independence in approximately 20%.²³¹

Future Trends

More widespread application of pancreas transplantation is expected in the future, with earlier transplantation indicated in the course of diabetic disease.¹⁴³ Successful trans-

plantation of human fetal pancreatic tissue into recipients who have type 1 diabetes is under investigation.⁴¹ Strategies to reduce the metabolic consequences of hyperglycemia on nerves and to enhance axonal regeneration are being studied.²⁴³

As previously mentioned, pancreatic islet beta-cell transplantation may replace whole-organ transplantation or may be used in combination with kidney transplantation or after pancreas transplantation failure.⁹⁵ Xenogeneic sources of cells, engineered islet cells with genes that induce immunoprotection, some form of beta-cell replacement therapy, and sustaining populations of transplanted beta-cells are all part of current research.⁸⁸

Four clinical trials of porcine islet transplantation have been reported with verbal reports of larger clinical trials already taking place in China and Russia. The Ethics Committee of the International Xenotransplantation Association is concerned about the need to complete studies in nonhuman primates before clinical trials are started. There is also concern about monitoring the transfer of porcine microorganisms.²⁶⁵

SPECIAL IMPLICATIONS FOR THE THERAPIST 21-7

Pancreas Transplantation

PREFERRED PRACTICE PATTERNS (ASSOCIATED WITH DIABETES MELLITUS AND IMMUNOSUPPRESSANTS)

4A, 4B: Primary Prevention/Risk Reduction for Skeletal Demineralization; Impaired Posture

5G: Impaired Motor Function and Sensory Integrity Associated with Acute or Chronic Polyneuropathies

6A: Primary Prevention/Risk Reduction for Cardiovascular/Pulmonary Disorders

6B: Impaired Aerobic Capacity/Endurance Associated with Deconditioning

7A: Primary Prevention/Risk Reduction for Integumentary Disorders

7B: Impaired Integumentary Integrity Associated with Superficial Skin Involvement

Neurologic function is often impaired in the person with diabetes mellitus. The first line of treatment for diabetic neuropathy has always been meticulous control of blood glucose to delay the onset of neuropathy and to slow its progression. The most physiologic means of achieving glycemic control is through pancreas transplantation, with resultant improvement in clinical and electrophysiologic measures of motor and sensory function and slightly improved autonomic function.²⁴³

Exercise

Information about exercise and activity following pancreas transplantation remains limited (see also the section on Exercise, Activity, Sports, and Organ Transplantation in this chapter). Pretransplant protocols follow an exercise program for an individual with diabetes. Posttransplant denervation of the donor pancreas and its relation to decreasing insulin secretion during exercise have not been adequately studied.²⁶⁰

Intestine Transplantation

Overview

In contrast to renal and liver transplantation, only a limited number of pancreas and intestinal live-donor transplants have been reported. The first intestinal transplantation, a segment of ileum from mother to child, was performed in 1964; the recipient died only 12 hours after surgery. Subsequent transplant recipients lived for days to weeks with continued progress until the 1990s, when long-term survival became possible. Research to develop tissue-engineered intestine that can be grafted to the small bowel is underway using animal models.^{159,169}

Indications and Prognosis

Replacement of multiple digestive organs simultaneously, termed *cluster operation*, was introduced to treat two diseases: locally confined gastrointestinal tumors and short-gut syndrome. Short-gut syndrome (short-bowel syndrome) is the malabsorptive state that often follows extensive resection of the small intestine or, more rarely, congenital shortening of the bowel structures.

Management of clients with irreversible intestinal failure from this or other causes includes total parenteral nutrition (a technique for meeting a person's nutritional needs by means of intravenous feedings, sometimes referred to as hyperalimentation), which may lead to liver failure and subsequent need for replacement of the liver, pancreas, stomach, duodenum, and jejunum. In children, multivisceral transplantation has been performed with some success for short-gut syndrome resulting from necrotizing enterocolitis or midgut volvulus.

Long-term graft survival exceeds 50% in large series, with better outcome for isolated intestinal grafts than for combined liver and small-bowel transplants. Limiting factors are infections (responsible for 60% of graft losses), technical and management errors (22%), and rejection (14%).³⁰⁶

Skin Transplantation

Human cadaver allograft skin is widely used for covering excised burn wounds when limited available skin donor sites or the overall client condition does not permit immediate grafting with autologous skin. However, recurring problems are associated with human cadaver allograft skin, including limited supply, variable quality, ultimate immune rejection, and the potential for bacterial and viral disease transmission.

Several biotech companies are working on tissue-engineered skin substitutes that could revolutionize the treatment of severe burns as well as pressure ulcers and other serious wounds. Engineers can now mass produce postcard-size sheets of durable, uniform tissue that the body readily accepts. Cells can be grown on biodegradable lattices to produce the functional equivalent of dermis and epidermis.

The FDA has already approved products for use in burn cases requiring immediate closure of wounds but where there is not enough undamaged skin to be used as autografts. These products are also approved in Europe

for plastic and reconstructive surgery and for the treatment of excisional wounds.

One type of patch is made up of two layers; the chemicals within the bottom layer help the new cells form a pattern similar to the normal dermis instead of the normally developing pattern of scar tissue. As dermis cells regenerate, blood vessels grow into this microscopic scaffolding over a 7- to 10-day period.

Within 3 weeks, the scaffolding dissolves as the new dermis grows in under the top layer of silicone. Acting as a pseudoepidermis, these patches close the burn injury to invading bacteria much like a normal skin graft would do.⁴⁶ Later, the top silicone layer can be pulled away easily for skin grafting.

Another type of newly developing artificial skin product is dermal fibroblast cells (connective tissue in the skin that produces collagen and elastic fibers) constructed from the foreskin of newborns and cultured onto a mesh that serves as the scaffolding. During the formation of tissue, the fibroblasts proliferate within the mesh, where they secrete human dermal collagen, matrix proteins, and growth factors.

One foreskin the size of a postage stamp can produce as many as 200,000 grafts. The separation process discards the immune stimulating cells and saves the fibroblasts (stimulate growth and regeneration of the dermis) and keratinocytes (provide protective epidermis). It takes approximately 6 days for the layer of dermis to grow, at which time the keratinocytes are added forming the tough outer layer known as the *stratum corneum*, which is capable of resisting injury and infection. The complete process takes approximately 20 days.

In both types of artificial skin products, the patches act as a template or scaffolding on which new dermis cells can form, allowing early wound excision and immediate wound closure with control of fluid loss. Reduced cases of rejection and reduced risk of infection and disease transmission potentially allow for early ambulation, earlier rehabilitation, and faster recovery.

Recognizing wound infection after graft application can be challenging because the graft appears white or yellow after hydration with wound fluid. Any change from baseline at the wound site; in the amount or type of edema, erythema, drainage, odor, and warmth; unex-

plained fever; or pain should be reported to the physician.

Normal skin grafting is still necessary for burns, but the new developing dermis allows surgeons to place over the wound a thinner, smaller skin graft from donor sites that heal within 1 week. Temporary skin replacement for excised burn wounds before autografting has been attached as long as 74 days without rejection and without hypertrophic scarring.

The drawbacks to this procedure are the cost (approximately \$1000 for one 4- to 10-inch sheet) and patch fragility, making the grafts difficult to work with and more easily dislodged than skin grafts. Researchers are continuing to explore the concept of an off-the-shelf full-thickness skin product that would be a permanent replacement for skin.

Ovary Transplantation

Although there has been one case of ovarian tissue transplantation, this is not an established procedure at the present time. The successful results of numerous studies involving removal of ovarian tissue, deep freezing (cryotherapy) the tissue, and subsequent reimplantation of the thawed tissue using animal models have been reported.¹⁷² Cryopreservation of oocytes and the banking of ovarian tissue for women who require conservation of fertility are being investigated.⁸⁵

These developments hold the hope of restoring fertility to young women who must have their ovaries removed because of noncancerous disorders such as cysts or endometriosis or who face infertility as a side effect of chemotherapy for cancer. The number of potential candidates is growing as long-term survivorship after high-dose chemotherapy and bone marrow transplantation rises.

References

To enhance this text and add value for the reader, all references are included on the companion Evolve site that accompanies this text book. The reader can view the reference source and access it online whenever possible. There are a total of 340 cited references and other general references for this chapter.

SECTION 3 PATHOLOGY OF THE MUSCULOSKELETAL SYSTEM

CHAPTER 22

Introduction to Pathology of the Musculoskeletal System

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The new century, characterized by increasing individual participation in high-speed travel, complex industry, and competitive and recreational sports, also is marked by significant increases in primary musculoskeletal system injury and conditions that have enormous impact on society.

The fact that the skeletal system with its associated soft tissues provides a protective covering for important structures such as the brain and heart and essentially makes up the limbs puts this system at risk for traumatic and repetitive insults and injuries (Box 22-1).

More than ever, the gap between science and clinical applications of therapeutic exercise has been narrowed. New diagnostic technology, the genome project, and a new branch of study called genomics are providing an increasing understanding of the molecular basis for disease and injury. This new knowledge is changing the approach for health care intervention in many areas, including the musculoskeletal system.

The ability to document the influence and effects of exercise at the molecular and cellular levels has resulted in early functional rehabilitation, preventive exercise programs, and the use of exercise as first-line intervention for many conditions. Maintaining good musculoskeletal health and recovering quickly from musculoskeletal injury or disease contribute to an individual's overall health, welfare, and quality of life.

Better technology has made it possible to measure what happens to muscle with age without painful and invasive muscle biopsies. For example, newer imaging methods are measuring fatty infiltration of skeletal muscle, a contributor to metabolic problems and muscle dysfunction with aging. Magnetic spectroscopy (MRS) and computerized tomography (CT) are being used to characterize this fatty infiltration. Scientists are looking for ways to reduce the risk of falls, fractures, and disability from changes in the supportive and protective skeletal muscle. Intervention strategies including various kinds of exercise are under investigation.

Preclinical disability is a new concept observed in aging adults (65 years of age or older). It is defined as progressive and detectable but unrecognized decline in physical function.⁴⁵ Early signs of decline in physical

function are observed in the ability to perform mobility tasks and activities of daily living needed to maintain an independent living status.¹⁸

Preclinical disability may be seen as an increased time to complete a task, modification of a task, or decrease in the frequency with which a task is performed. Individuals with preclinical disability are at increased risk for progression to more severe disability; early identification of decline in physical function is important if intervention to stop the decline is possible.^{44,45}

More than 50% of injuries in the United States are to the musculoskeletal system; 28.6 million Americans incur musculoskeletal injuries each year. Fractures, sprains and strains, and dislocations account for nearly half of all musculoskeletal injuries.

Annually, an estimated 7 million Americans receive medical attention for sports-related injuries.²⁸ Children younger than 15 years old account for more than 3.8 million sports-related injuries in the United States each year. Violence-related sports and recreational injuries (e.g., being pushed, hit) are increasing among children and adolescents.²⁷ See the section on Occupational Injuries and Diseases in Chapter 4.^{8,22}

Severe cerebral palsy and other developmental disorders (see Chapters 23 and 35) are more common than ever before, because many infants with these complications at birth now survive and live into adulthood. The age span of humans has become progressively longer, with a variety of accompanying age-related conditions such as osteoporosis and degenerative joint or disc disease. Arthritis is the leading chronic condition reported by Americans age 65 years and older.⁷⁸

In addition, the musculoskeletal system often is confronted with immobilization secondary to major illness or injury, bed rest, or casting or splinting of a specific body region. The musculoskeletal system reacts quickly to the lack of mechanical stress and normal loading (immobilization) in ways that may adversely affect recovery and rehabilitation.

The physical and physiologic responses of the musculoskeletal tissues and resultant deterioration occur within days but take many months to reverse. In fact, 3 weeks of bed rest has a more profound impact on physical work

Box 22-1**COMMON MUSCULOSKELETAL DISORDERS**

- Fracture
- Dislocation
- Subluxation
- Contusion
- Hematoma
- Repetitive overuse, microtrauma
- Strain, sprain
- Degenerative disease

capacity than three decades of aging.^{37,46} See the section on Tissue Response to Immobilization in Chapter 6; see Table 6-7.

Like all other body systems, the musculoskeletal system does not function in isolation. Therefore, primary disease of the musculoskeletal system can significantly affect other body systems and vice versa. In addition, certain diseases are systemic, meaning that all body systems, including the musculoskeletal system, can be involved to some degree. The challenge to develop an effective rehabilitation program is heightened when one is faced with complex, multisystem disorders (see Chapter 5).

Many musculoskeletal disorders are drug induced or are side effects of treatment for conditions such as cancer. Drug-induced musculoskeletal disorders represent a broad clinical spectrum, from asymptomatic biologic abnormalities to severe and even life-threatening diseases. Myopathies, arthralgias, arthropathies, connective tissue diseases, and periarticular disorders (e.g., tendinopathy, enthesopathy, adhesive capsulitis) have been linked with medications. An increasing number of drugs have been implicated in inducing rheumatic symptoms and/or syndromes. All drug classes can induce musculoskeletal disorders, but the majority are caused by corticosteroids, vaccines, antibiotics, and lipid-lowering agents.¹²

The purpose of this section is to provide an overview of the musculoskeletal system, including the biologic response to trauma and examples of how primary diseases in other organs affect the musculoskeletal system, and vice versa, and to begin to examine the local (musculoskeletal) and systemic (e.g., immune system, endocrine system, gastrointestinal system) effects of exercise. An approach that assesses all the systems and considers underlying pathology is essential when identifying the source of dysfunction.

ADVANCES IN MUSCULOSKELETAL BIOTECHNOLOGY

Over the past 10 years, advances in molecular biology techniques have extended the potential for understanding musculoskeletal disorders from the microscopic (histologic) level down to the molecular level of gene expression within individual cells. These advances are initiating new avenues of research and, ultimately, novel clinical interventions.⁶

Orthopedic surgery has been revolutionized by tissue engineering, including biologic manipulation for spinal fusion³⁰; synthetic skeletal substitute materials¹²; preservation and restoration, transplantation, or fabrication of avascular tissue (e.g., meniscus, articular cartilage)^{71,80}; and joint restoration instead of joint replacement.⁵⁵

Other technologic advances are under scientific investigation, such as bone implants to stimulate bone development and prevent limb loss associated with cancer^{16,89}; injectable bone substitute that eliminates the need for bone grafts, strengthens osteoporotic vertebral bodies, or heals compression and nonunion fractures^{33,36}; synthetic muscle regeneration; and new materials and plastics making it possible to replace spinal discs or extend joint replacements by an additional 10 years or more.

Recently the influence of biopsychosocial-spiritual stress on the physical body has come to the forefront of research in a field of study referred to as psychoneuroimmunology. Approximately 40% to 80% of adults in primary care report only their physical symptoms (including musculoskeletal manifestations), leaving a large portion of clients with significant psychologic distress undiagnosed.⁵⁷ Physical therapists often see clients demonstrating various somatoform disorders (see Chapter 3); recognizing this underlying component is important in understanding the biology (and pathology) of the musculoskeletal system and therefore planning appropriate intervention.

Gender discrepancies in rates of injuries and muscle mass response to strength training or deconditioning are also under investigation.^{11,30} Differences in ligamentous laxity, muscle strength, endurance, muscle reaction time, and muscle recruitment time in males versus females and athletes versus nonathletes may provide additional important information for prevention and rehabilitation of musculoskeletal injuries.⁶¹

Women double their rate of injury during ovulation, when levels of estrogen are the highest. Training and conditioning differently during different times of the month may help protect women from injury.^{24,31,53} The effectiveness of neuromuscular and proprioceptive training in preventing anterior cruciate ligament injuries in female athletes has been demonstrated.⁶³

Men increase their muscle volume about twice as much in response to strength training compared with women; men also experience larger losses in response to detraining than women.^{56,64}

The military has recognized that females undertaking strenuous exercise alongside males are at increased risk of injury. Equal opportunities legislation has been interpreted to require identical training for males and females, but some segregation of training may be necessary to reduce the excess risk of injury to females, provided the outcome of training is no less favorable to either gender.¹⁵

BIOLOGIC RESPONSE TO TRAUMA

See also Specific Tissue or Organ Repair in Chapter 6.

The immediate biologic response to trauma is a generalized inflammatory reaction regardless of what tissue