Infection and cardiac rejection are the most significant causes of morbidity and mortality after heart transplantation. At some transplant centers, more than half of the early transplantation-related deaths are the result of infection. The infectious agents may be transmitted to the host by means of the allograft, through blood transfusion, by nosocomial or environmental routes, or they may represent endogenous microbial flora or reactivation of a prior infection. The frequency of infectious complications is generally related to the degree of immunosuppressive therapy required to prevent graft rejection. Both the composition of the immunosuppressive regimen and the dosage of the immunosuppressive drugs affect the infection rate. Recent protocols, employing a combination of cyclosporine, steroids, and azathioprine cause less toxicity and lower infection rates than protocols that rely solely on cyclosporine and steroids or protocols utilized in the 1970s, which did not contain cyclosporine. A literature review of data reported from 12 transplant centers, encompassing 384 patients who received their transplantation in the era of cyclosporine, revealed infections in 221 patients (57.6%), with 20 infection-related deaths (5.2%). All classes of microorganisms infected the heart transplant recipients. The most frequent agents included staphylococci, gram-negative enteric, Nocardia (bacterial); Aspergillus, Candida, Cryptococcus (fungal); cytomegalovirus, herpes simplex, herpes zoster (viral); and Pneumocystis carinii, Toxoplasma gondii (protozoal). The respiratory tract, urinary tract, and skin were the most common sites of infection. Most infection-related fatalities were caused by bacterial sepsis, Aspergillus, or cytomegalovirus. At present, the lowest infection rates in these patients may be achieved by careful control of immunosuppressive therapy, infection control procedures, rigid criteria for diagnosing rejection, and by monitoring patients with techniques that permit early identification of infection. J HEART TRANSPLANT 1988;7:390-4.

Recipient of organ allografts confront graft rejection and infection as two major challenges to their long-term survival. Rejection, the most significant factor limiting successful transplantation, can usually be controlled by treating the patient with combinations of cyclosporine, corticosteroids, azathioprine, antithymocyte globulin, and murine antihuman mature T cell (OKT3). These immunosuppressive agents minimize the humoral and cell-mediated responses that are directed against the graft. To a large extent the improved survival rates observed in organ transplant recipients have paralleled the ability of physicians to control the immune response, with the introduction of cyclosporine in 1980 being the major advance. Manipulation of the immune system, however, is not without adverse consequences. Infection, the other major challenge of successful transplantation, shares an interesting relationship with graft rejection, as efforts to control the latter (increased immunosuppressive therapy) often lead to more frequent or more severe infection.

Clearly, immunosuppressive therapy must be carefully balanced to limit the extent of both infection and graft rejection. In this article we discuss the factors that influence infection in heart transplant recipients, the most common causative organisms, and methods that aid in the diagnosis of infection.

**SCOPE OF THE PROBLEM**

Although rejection-related morbidity has declined since the introduction of cyclosporine, infection remains the...
Infection and Heart Transplantation

TABLE I Infectious complications of heart transplantation at selected transplant centers*

<table>
<thead>
<tr>
<th>Institution</th>
<th>Transplantations</th>
<th>Patients with infections (%)</th>
<th>Infection-related deaths (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanford University</td>
<td>72</td>
<td>32 (44)</td>
<td>8 (11)</td>
<td>3</td>
</tr>
<tr>
<td>University of Pittsburgh</td>
<td>17</td>
<td>11 (65)</td>
<td>3 (17)</td>
<td>13</td>
</tr>
<tr>
<td>Texas Heart Institute</td>
<td>18</td>
<td>14 (78)</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Loyola University</td>
<td>76</td>
<td>51 (67)</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Emory University</td>
<td>43</td>
<td>18 (42)</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>St. Vincent’s Hospital, Australia</td>
<td>27</td>
<td>31 (85)</td>
<td>1 (3)</td>
<td>7</td>
</tr>
<tr>
<td>Clinica Puerta de Hierro</td>
<td>35</td>
<td>13 (37)</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Multinstitutional, Utah</td>
<td>28</td>
<td>11 (39)</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>St. Louis University</td>
<td>21</td>
<td>6 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humana Heart Institute</td>
<td>16</td>
<td>16 (100)</td>
<td>2 (13)</td>
<td>10</td>
</tr>
<tr>
<td>University of Ottawa</td>
<td>11</td>
<td>7 (64)</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Cincinnati</td>
<td>10</td>
<td>11 (100)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>384</td>
<td>221 (57.6)</td>
<td>20 (5.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Institutions selected on the basis of availability of data in published literature, with immunosuppressive protocols containing cyclosporine (after 1980).

Major cause of morbidity and mortality in organ transplant patients. Most deaths during the first year after transplantation, for example, are attributable to infection rather than to operative or hemodynamic complications. Infection rates and infection-related mortality vary considerably between transplant centers. The data summarized in Table I reflect infection rates of heart transplant patients treated with cyclosporine reported from 12 institutions since 1980. The reported rate of documented infections was 57.6% (range, 29% to 100%). This is likely an underestimation, which does not include patients with mild infection (discussed below). The infections occurring among these patients were usually treatable, as only 20 of 349 patients (5.2%) had infections that contributed to their deaths (Table I).

Types of Infections

Immunosuppressed individuals are, in general, susceptible to infection by any microorganism, including those that are not generally considered to be pathogens. Thus any listing of infectious agents affecting these patients is inherently incomplete. A wealth of experience, however, has been gained from the many patients who have undergone heart transplantation. The most common pathogens of these individuals are as follows:

Bacterial
- Gram-negative enteric
  - *Legionella*
  - *Nocardia*
  - *Staphylococcus*

Fungal
- *Candida*
- *Aspergillus*

Viral
- *Cytomegalovirus*
- *Herpes simplex*
- *Varicella zoster*
- *Hepatitis B*

Protozoal
- *Pneumocystis*
- *Toxoplasma*

Bacterial infections account for most infections early after transplantation. Gram-negative enteric bacteria, such as *Escherichia coli*, enterococci, and *Pseudomonas aeruginosa* are among the most frequent pathogens, particularly as a cause of pneumonia or urinary tract infections. Many of these infections are facilitated by the vascular lines and urinary bladder catheterization required after transplantation, as the incidence of bacteremia in heart transplant patients is similar to non-immunosuppressed patients in intensive care facilities. Depressed pulmonary function caused by chronic congestive heart failure, however, contributes to the susceptibility of these patients to pneumonia. Although fatal bacterial sepsis is uncommon because of antibiotic therapy, it may occur.

The spectrum of viral, fungal, and protozoal infection in the heart transplant patient is similar to that seen in patients who are receiving immunosuppressive therapy to support kidney or liver allografts, or those who have received cytotoxic therapy in conjunction with...
bone marrow transplantation. Susceptibility of these pathogens reflects depressed cell-mediated immunity, a particular problem in the immediate posttransplantation period, and during episodes of graft rejection, when dosages of immunosuppressive drugs are intensified.

Cytomegalovirus (CMV) infection is a particular problem in heart transplantation. Dummer et al., from the University of Pittsburgh, reported a CMV infection rate of 100%, with 36% of patients being asymptomatic and 79% having CMV viremia. Hofflin et al., of Stanford University, Stanford, California, observed CMV infection in 25% of patients. Both groups found that CMV infection was usually caused by reactivation of prior infection, as infection rates were highest in individuals with positive results of serologic tests. As discussed below, CMV harbored in the donor heart or in blood products is an important cause of infection in recipients who have negative results from serologic tests for CMV. Reactivated Epstein-Barr virus infection may also occur during immunosuppressive therapy and may be associated with the development of non-Hodgkin's lymphoma. Other herpes viruses (herpes simplex and herpes zoster) may cause mucocutaneous infection.

Infections with Aspergillus are a major cause of mortality in individuals with depressed cell-mediated immunity. Among heart transplant patients, Aspergillus infections, which usually are pulmonary based, have a high mortality despite therapy with amphotericin B. Pneumocystis carinii is a well described pathogen of the immunosuppressed host. This parasite infects approximately 3% of heart transplant recipients. Interestingly, this percentage is similar to the estimated prevalence of this organism in asymptomatic individuals who are "colonized" with P. carinii.

Toxoplasma gondii infection is a well recognized complication of heart transplantation, which may occur as a primary or reactivated infection. Primary infection, which is usually transmitted by means of the donor organ, carries a high mortality unless promptly treated.

The question of what constitutes an adequate infection control procedure is controversial. Approaches have ranged from complete reverse isolation with laminar airflow to housing the patient in open wards. Hospital staff members are quite opinionated on this question, usually without strong data to support their view. Many programs initially adopt the isolation guidelines used for bone marrow transplant patients, such as positive-pressure rooms with efficient particulate filters, with staff members and visitors wearing gowns, hoods, masks, boots, and gloves until the patient's T-lymphocyte count returns to normal. When one considers the pathogens that commonly infect the transplant patient, it becomes clear that infection control guidelines may be quite limited in controlling infection. Most of the infections occurring in these patients are not acquired from external sources but represent organisms that are indigenous to the patient, that is, staphylococci on skin, enteric bacteria, and latent viruses. When the patient receives immunosuppressive therapy, the patient's normal flora provides a large reservoir of pathogens. For this reason, urinary catheters, vascular lines, and endotracheal tubes should be removed as soon as feasible, as these often serve as routes for passage of infection.

Prophylactic antibiotics are utilized in most transplant procedures. Most physicians will utilize broad-spectrum antimicrobials, such as cephalosporins, penicillin G, and/or streptomycin. Acyclovir has been used as a prophylactic for CMV infection but has not been beneficial. 9-(1,3-Dihydroxy-2-propoxy-methyl)-guanine (DHPG), a guanine analog with anti-CMV properties, is effective for the treatment of active CMV infection, but its prophylactic use has not been investigated. Prophylaxis for P. carinii infection is readily provided by trimethoprim-sulfamethoxazole, although the incidence of P. carinii has been low among heart transplant patients, even without prophylaxis.

Infection rates are also influenced by more subtle factors. The drugs comprising the immunosuppressive protocol and the dosage of these drugs have a strong influence on the infection rate after heart transplantation. A study by Barnhart et al., comparing conventional immunosuppressive therapy (azathioprine, antithymocyte globulin, and prednisone) with a protocol employing cyclosporine and prednisone revealed fewer infections in the latter protocol, without increased rejection. Studies by Dresdale et al., showed that with lower dosages of cyclosporine and oral prednisone for maintenance, immunosuppression resulted in an infection rate of 0.23/patient as compared with 0.82 to 1.06/patient when higher dosages of steroids were used.

FACTORS INFLUENCING INFECTION

The infection rates from 12 centers are summarized in Table I and range from 29% to 100%. There are several plausible explanations for these widely varying infection rates. Obvious factors include (1) variance or imprecision in the definition of infection, which may be further modified by the term clinically significant, (2) difference in infection control procedures, and (3) variation in the use of antibiotic prophylaxis. These factors will influence the infection rate among all groups of hospitalized patients, without regard to transplant status or immunocompetence.
In a recent report from the University of Minnesota, Minneapolis, Andreone et al. calculated infectious complications in patients receiving three different immunosuppressive protocols: (1) antithymocyte globulin, prednisone, and azathioprine; (2) high-dosage cyclosporine and prednisone; and (3) low-dosage cyclosporine, prednisone, and azathioprine. Similar infection rates were observed with protocols 1 and 2 (1.3 episodes/patient and 1.6 episodes/patient, respectively). Patients receiving protocol 3 had an infection rate of 0.6/patient. Although the proportion of viral infections seems greater in patients receiving the three-drug regimen, these patients also had a lower rejection rate, a factor that further influences the rate of infections.

In the 1970s, Mason et al. observed nearly a threefold increase in the occurrence of infection during periods of intensification of immunosuppressive therapy to control acute rejection. Considering the balance between the control of rejection and infection, this observation is not surprising. Less obvious is the notion that the accuracy of the rejection diagnosis influences the infection rate. Because this diagnosis is usually made by histologic interpretation of biopsy material, a process that is inherently subjective and imprecise, the potential for overtreatment exists. Endomyocardial biopsies obtained soon after transplantation may reveal ischemic myofiber necrosis, which could be confused with moderate and/or severe rejection. When rejection is present, the possibility of interobserver and intraobserver variation exists, so that mild rejection, which may not be immediately treated in patients receiving cyclosporine, could be interpreted as moderate rejection and usually mandates treatment. An additional problem is distinguishing rejection and endomyocardial infection. CMV and T. gondii infection may cause intense myocardial inflammation that mimics severe rejection. It is also possible that such infection may coexist with graft rejection. Clearly, optimum patient care requires caution and expertise in the interpretation of endomyocardial biopsies.

DIAGNOSIS OF INFECTION

Several approaches and/or methods aid in the identification and management of infection in heart transplant patients. Pretransplant serologic studies for CMV, Epstein-Barr virus, and T. gondii indicate whether the patient is at risk for primary or reactivation infection with these organisms. With this information prophylaxis for toxoplasmosis or the use of blood products that are seronegative for CMV may be considered.

The diagnosis of pulmonary infection is particularly important in heart transplant patients. The lung is a common site of infection, and pulmonary infection may adversely alter the patient’s hemodynamics. Sputum cultures, transtracheal aspiration, transbronchial biopsy, transthoracic biopsy, open-lung biopsy, and bronchoalveolar lavage are often employed to obtain material for microbial culture or histologic studies. The yield of diagnostic material is lowest from sputum or tracheal secretions, since these specimens do not necessarily mirror the lower respiratory tree. Transbronchial and open-lung biopsy specimens usually provide adequate material for study but carry the risk of hemorrhage or the morbidity associated with an additional thoracotomy.

Bronchoalveolar lavage, a technique whereby samples of the lower respiratory tree are obtained by instillation of sterile saline solution through a flexible fiber-optic bronchoscope, is well suited to the diagnosis of pulmonary infection. The technique has proved reliable in the identification of P. carinii, CMV, herpetic trachoeobronchitis, Aspergillus, and other pulmonary pathogens in patients with acquired immunodeficiency syndrome or immunodeficiency caused by treatment with cyclosporine or by cytotoxic therapy. Because of its high diagnostic yield, rapidity, and low morbidity, bronchoalveolar lavage is well suited to the diagnosis of infection or as a method of screening patients before transplantation.

SUMMARY

Experience from over 3000 heart transplantations performed worldwide has taught the medical community that virtually any microorganism may infect the transplant patient. The incidence of infection is influenced by many factors, but the key to a low rate of infection is judicious immunosuppression, sufficient to protect the graft from rejection but not so bold as to render the patient prey to all microorganisms. Recent refinements in drug protocols, particularly the implementation of multiple-drug, low-dosage immunosuppression, results in lower infection rates. Further refinements in the control of rejection, including the development of more selective immunosuppressive drugs, will further reduce infection-related mortality.

ACKNOWLEDGMENTS

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