

# Infection in the Bone Marrow Transplant Recipient and Role of the Microbiology Laboratory in Clinical Transplantation

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## INTRODUCTION

As bone marrow transplantation (BMT) and solid organ transplantation have evolved to become the preferred treatment options for a number of malignancies and end-stage organ dysfunctions, these forms of therapy are now limited more by organ availability than by technical skill or lack of adequate immunosuppression. Despite the success of transplantation medicine, a problem that continues to plague the

transplant recipient is that of infection, which remains the leading cause of death in this population (54, 224, 225, 299). With more widespread use of transplantation, often in the treatment of increasingly ill patients, and with more prolonged survival of these patients, infection will probably present an even greater challenge in the future.

The clinical microbiology laboratory plays an essential role in the diagnosis and management of infection in the transplant patient. Indeed, any institution with a transplantation program requires optimal diagnostic microbiology services for providing physicians with accurate and timely information during all phases of the transplantation process (18, 286). More extensive use of transplantation will require laboratories, in both aca-

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demic and community settings, to provide resources necessary for the rapid diagnosis of infection. Furthermore, laboratories will be called upon to deliver the technological and logistical means for meeting these demands in an economic climate of cost containment. This review will discuss infection in the transplant recipient, with a focus on BMT, and the role of the clinical microbiology laboratory in clinical transplantation.

## EVOLVING RISK FACTORS FOR INFECTION IN THE TRANSPLANT RECIPIENT

### Bone Marrow Transplantation

The principle behind BMT for malignant and nonmalignant hematologic diseases is the ablation of abnormal marrow followed by the rescue of marrow function by replacement of the ablated marrow elements with normal donor marrow (14). BMT begins with conditioning therapy in which marrow-toxic high-dose radiation and/or chemotherapy is given. This conditioning therapy destroys malignant cells and suppresses host immunity to prevent rejection of donor cells. Following effacement of the diseased native marrow, an intravenous infusion of donor marrow is administered. Donor marrow is obtained by multiple aspirations from the posterior iliac crest of a genetically related individual. This is allogeneic BMT. The extent of HLA matching between the donor and recipient is one factor determining the severity of rejection of the donor marrow by the host and reaction of the donor marrow to the host, i.e., graft versus host disease (GVHD). The outcome is thus influenced by the degree of HLA relatedness (22).

Autologous BMT is used in the treatment of certain solid organ malignancies as well as lymphoproliferative disorders. In autologous BMT, the BMT recipient also serves as the bone marrow donor. Normal marrow or stem cells are harvested from the patient's marrow or peripheral blood. If conventional treatment modalities fail, high-dose chemotherapy and/or radiation is administered with the goal of completely eradicating malignant cells from the body. A secondary effect is destruction of marrow cells. The patient's previously harvested marrow is then reinfused, thus restoring bone marrow function. Rejection and GVHD are not a major problem in autologous transplantation, because the patient's own marrow is used. The most significant complication is relapse of the original disease and infection during the period of intense immunosuppression. The number of autologous transplants per year now exceeds that of allogeneic transplants (11).

The period of immune system reconstitution after BMT (14, 148, 222, 231) is somewhat variable in progression and duration and may not conclude for a year or more after transplantation. This reconstitution is influenced by multiple factors and in turn strongly influences the risk of infection throughout the posttransplantation period. In the early period after transplantation, a combined immunodeficiency state is found as both cell-mediated immunity and humoral immunity are lost. Although the cell number returns to normal, phagocyte function and immunoglobulin production may be defective for over a year following transplantation. The rate and completeness of immune recovery are influenced by the type of allograft, the degree of histocompatibility mismatch, the conditioning regimen, the presence or absence of GVHD, and possible infection with immunomodulating viruses. These factors are considered in the development of differential diagnoses for infection in the posttransplantation period, in the selection of appropriate prophylactic antibiotic regimens, and in the timing of posttransplantation immunization schedules.

Susceptibility to infection reflects this progressive change in

TABLE 1. Evolving risk of infection in the bone marrow recipient

Time	Infectious agent
Early (neutropenic period) .....	Bacteria
	Common gram-positive and gram-negative pathogens
	Fungi
	<i>Candida</i> spp.
	<i>Aspergillus</i> spp.
	<i>Fusarium</i> spp.
Middle (following marrow recovery) <sup>a</sup> .....	Viruses
	CMV
	VZV
	HHV-6
	Adenovirus
	RSV
Late (>100 days post-transplantation) .....	Fungi
	<i>Aspergillus</i> spp.
	<i>P. carinii</i>
	Protozoa
	<i>T. gondii</i>
	Bacteria
<i>S. pneumoniae</i>	
<i>S. aureus</i>	
	Viruses
	VZV
	CMV
	RSV
	Fungi
	<i>P. carinii</i>
	Protozoa
	<i>T. gondii</i>

<sup>a</sup> More common in patients experiencing GVHD or infection with immunomodulating viruses.

the immune status of the host. Consideration of these variables helps the clinician to direct microbiological studies aimed at the diagnosis of infection. In addition to the rapidity of immune system reconstitution, factors influencing the risk of infection in the BMT recipient include the type of pretransplantation conditioning regimen, the extent of injury to mucosal barriers by chemotherapy and GVHD, infection with immunomodulating viruses, and often an underlying immunodeficiency imposed by malignancy.

The posttransplantation period may be divided into phases of different risks of infection based upon the pattern of immune system recovery (30, 155) (Table 1). The early phase following transplantation is determined by the duration of neutropenia. Infections at this stage are those common to any neutropenic host, and the pathogens most often encountered

are bacteria, *Candida* spp., and herpes simplex virus (HSV). The next phase, following marrow engraftment and typically including the second and third posttransplantation months, is dominated by viral and fungal pathogens. Cytomegalovirus (CMV) infection has been a major problem in BMT patients at this stage. If neutropenia has been prolonged, the risk of infection with opportunistic fungal pathogens such as *Aspergillus* spp. rises dramatically (91, 155, 221). After the first 100 days, the risk of infection is dependent upon the rapidity of complete immune system recovery as well as the possible immunosuppressive pressures of GVHD and infection by immunomodulating viruses (16, 156, 182, 223, 266). In view of the delayed immune system recovery as described above, it is not surprising that these patients often have problems with infection long after transplantation. In a study of late infections in long-term survivors of BMT, only 34% remained free of infection 6 months or longer after transplantation (16). Agents commonly encountered in this late period include bacterial pathogens such as *Streptococcus pneumoniae* and *Staphylococcus aureus* and the nonbacterial pathogens varicella-zoster virus (VZV), CMV, and *Pneumocystis carinii* (15, 16, 30, 156, 301).

### Solid Organ Transplantation

The risk of infection in the solid organ transplant recipient involves a fascinating evolution of immune system abnormalities to which the underlying disease, iatrogenic immunosuppression, presence of the foreign allograft, immunomodulating herpesviruses, and organ rejection contribute. The predictable sequence of infectious risk is well described by Rubin et al. in renal transplant recipients (228), and the principles also apply to the other transplant populations. In the first posttransplantation month, immunosuppression has just commenced and cumulative exposure to immunosuppressive drugs as well as exposure to environmental sources of infection is small. In addition, rejection and infection with immunomodulating viruses are usually not yet problematic. The risk of infection is therefore related largely to nosocomial bacterial pathogens that typically take advantage of the postoperative hospitalized patient. The only fungal pathogens commonly encountered during this time period are *Candida* spp., and the only virus is herpes simplex virus (HSV). Types of infection include pneumonia, urinary tract infection, intravenous catheter-related infection, and wound infection. Rarely, the allograft harbors pathogens and is itself a source of infection (95, 242, 247). Also encountered uncommonly is the emergence of a previously unrecognized latent pathogen that was present in the recipient prior to transplantation (79, 139, 215, 238, 256, 264).

Infection between the first and sixth months following transplantation is dominated by viral and fungal pathogens. Iatrogenic immunosuppression remains fairly intense during this time, and problems with graft rejection often arise, adding to the degree of immunosuppression. Opportunists thrive in this setting, and suspicion of infection with such organisms must be high.

In the late posttransplantation period, more than 6 months following transplantation, if problems persistent with rejection or chronic viral infection, the risk remains the same as in the second period; these patients remain at very high risk of opportunistic infection. If, however, the patient is clinically prospering and is on a stable immunosuppressive regimen with good allograft function, the risk of infection resembles that of any minimally immunosuppressed individual in the community. Opportunistic infection in this setting typically implies an intense environmental exposure (114, 224, 225, 228).

## INFECTION IN THE TRANSPLANT RECIPIENT

### Bacteria

**Common bacterial pathogens.** In the early posttransplantation period, the patient is at risk for bacterial infections commonly encountered in the hospital. The risk of bacterial infection in the BMT recipient is compounded by the profound neutropenia attendant on the procedure. Prior to marrow engraftment, these patients indeed have the same predilection for bacterial infection as do other neutropenic populations. The shift in the predominant organisms associated with infection in the neutropenic host from gram-negative to gram-positive bacteria has also been seen in the BMT population (30, 157), and in one study, gram-positive organisms represented 68% of all organisms causing bacteremia (30). Following engraftment and recovery of leukocyte numbers, *S. pneumoniae* is a significant cause of late pulmonary infections and bacteremia (30, 120, 157, 301), with an incidence of 27% in long-term survivors reported in one review (301). Early bacterial infections among solid organ recipients include ventilator-associated pneumonia, wound infection, urinary tract infection, mediastinitis, peritonitis, and intravenous line-related infection. Bacterial pneumonia remains the most frequent early infection among lung transplant patients, with *Pseudomonas* spp. and *Burkholderia cepacia* being the predominant pathogens (118, 150, 191). Renal transplant recipients are at a particularly high risk for bacterial infection of the urinary tract. The incidence may approach 80% without the use of prophylactic antibiotics (224, 225). Urinary tract infections in transplant recipients more commonly are complicated by pyelonephritis, bacteremia, and relapse than are those in other hosts (224, 225).

**Salmonella spp.** Non-typhoidal *Salmonella* spp. cause infection more commonly in immunocompromised than in immunocompetent persons. Infection is more likely to occur during periods of intense immunosuppression and is associated with episodes of rejection (67, 121, 232). Typically causing a mild gastrointestinal illness in immunocompetent persons, *Salmonella* spp. are more likely to cause bacteremia, seed multiple sites, and cause relapsing infection in transplant recipients (67, 121, 232). Focal manifestations include visceral abscesses, vascular infections, septic arthritis, pyelonephritis, and peritonitis (67, 232). It has also been suggested that infection may adversely influence allograft function (121).

**Listeria monocytogenes.** An organism deserving special attention when considering bacterial causes of infection in the transplant patient is *L. monocytogenes*. This organism is acquired through the gastrointestinal tract by ingestion of animal products or contaminated food. In the transplant recipient, infection with *L. monocytogenes* most commonly causes central nervous system (CNS) infection and primary bacteremia (12, 37, 143, 224, 262). Defense against the organism is dependent upon intact cell-mediated immunity (134). This infection appears in the middle or late phase following transplantation, and the risk is influenced by the use of prophylactic antibiotics as well as the degree of immunosuppression (12). In one series, 70% of patients with listeriosis had experienced recent rejection (262). *L. monocytogenes* is one of the most common bacterial causes of meningitis among renal transplant recipients (238). Nonmeningeal brain involvement, rarely found in groups other than transplant recipients (181), may be diffuse or focal (49, 262). There are other less common manifestations of listeriosis in the transplant population, which include myocarditis, pneumonia, and hepatitis (29, 262, 263).

**Legionella spp.** *Legionella* spp. are important pulmonary pathogens in the immunocompromised patient, including the transplant recipient. The incidence of infection varies geo-

graphically among transplant centers, depending upon the risk of exposure to the organism in a particular community or nosocomial environment, and in some centers *Legionella* spp. are the predominant bacterial pathogens (86, 87). Reports of the frequency of infection vary from 2% (208) to 17% (115) of recipients, and disease appears to occur throughout the post-transplantation period. The typical manifestation of pulmonary involvement by *Legionella*, with progression of a focal infiltrate to bilateral diffuse disease (172), may be less common among the immunocompromised. These patients often present with nonspecific symptoms and a paucity of pulmonary findings (253). Cavitory lung lesions, which are not a feature of disease in the normal host, have been found in immunocompromised patients (51, 297). As in other populations, extrapulmonary involvement has also been reported in transplant patients (253, 276).

***Nocardia* spp.** *Nocardia* spp. cause infection in patients with lymphoreticular malignancy, cell-mediated immune system defects, corticosteroid use, and a multitude of other immunocompromising conditions including organ transplantation. In one review, 13% of all nocardial infections occurred in organ transplant recipients (21), and in another, the frequency was 26% (298). *Nocardia* spp. are introduced via the respiratory tract or alimentary tract or by direct skin inoculation. They are most commonly acquired by inhalation, and pulmonary disease is the most common manifestation. Pulmonary findings include single or multiple nodules, focal pulmonary infiltrates with or without cavitation, and diffuse parenchymal involvement (10, 298). Dissemination from the lungs occurs, and common sites of secondary involvement are the brain and skin (10, 49, 89, 130, 298).

***Mycobacteria.*** Although the incidence of mycobacterial infection in the transplant population far exceeds that in the general population, it is relatively low in this group, estimated at approximately 2% in solid organ recipients and even lower in BMT recipients (131, 139, 173, 225, 255, 264). Disease may rapidly follow primary infection when exposure occurs after transplantation, it may occur as reactivation disease upon institution of immunosuppressive therapy in patients exposed to the organism before transplantation, or it may be transmitted by the donor organ itself with reactivation in the allograft following transplantation (139, 255, 264). Infection with *Mycobacterium tuberculosis* has been reported in both the early and late periods following transplantation (110, 139, 255, 264). The risk of mycobacterial infection appears to rise with episodes of rejection or GVHD (110, 131, 139, 173, 183), and a possible association with CMV infection (261) as well as nocardial infection (252) has been suggested.

In addition to the pulmonary and extrapulmonary disease (139) caused by *M. tuberculosis*, a substantial proportion of mycobacterial infection is caused by nontuberculous species. These mycobacteria are also likely to cause extrapulmonary disease (139, 183, 255), with a propensity for involvement of skin and soft tissues as well as joints (50, 89, 141).

## Fungi

**Risk of fungal infection.** Factors commonly predisposing to invasive fungal infection in the hospitalized patient include immunosuppression, administration of broad-spectrum antibiotics, long-term venous access devices, hyperalimentation, malnutrition, disruption of mucosal and skin surfaces, and recent major surgical procedures (55, 285, 293, 294, 311). Certainly, these risk factors apply to many transplant recipients. Among solid organ recipients, the incidence of invasive fungal infection ranges from 5% in kidney transplant patients (174, 243) to

greater than 20% in liver (35, 47, 285) and pancreas (144) recipients.

As neutropenia is a significant risk factor for candidal infection (31, 290), it is not surprising that BMT patients experience problems with *Candida* and other fungal pathogens in the early posttransplantation period while awaiting engraftment and return of functioning neutrophils (30, 94, 299) and that the duration of neutropenia correlates with the risk of infection (157). In the later periods following engraftment, fungal infection is most closely related to the presence of GVHD and subsequent use of corticosteroids (157, 299).

***Candida* spp.** The risk of candidal infection in the BMT recipient is closely linked to neutropenia, and, accordingly, the median time of onset is 1 to 2 weeks following transplantation (94, 299), during the period of agranulocytosis. Infection with *Candida* spp., which occurs in 10 to 25% of patients (94, 205, 299), is associated with a poor outcome—a mortality rate of 39% for candidemia alone and 90% when tissue invasion occurs (94). In the granulocytopenic BMT patient, candidiasis is often disseminated, with involvement of the liver, spleen, kidney, heart, gastrointestinal tract, lungs, skin, and brain (89, 117, 136, 249). Despite widespread involvement, clinical findings are typically nonspecific, making diagnosis difficult (299).

A form of disseminated infection described in the neutropenic host is hepatosplenic candidiasis (136, 274). Typically, the patient will have unexplained fever during the period of granulocytopenia and will then develop clinical evidence of hepatic involvement after the return of functioning neutrophils (274). Computed tomography or ultrasound shows multiple focal abnormalities in the liver and spleen, described as “bull’s-eye” lesions (98, 274, 284). Although the appearance of these lesions on imaging studies of the liver suggests involvement by *Candida* spp., they are identified premortem in only 13 to 23% of patients (220). Magnetic resonance imaging may be a more useful imaging modality for the evaluation of hepatosplenic candidiasis (41, 244). Liver biopsy or needle aspiration may support the diagnosis by revealing granulomas and microabscesses with typical fungal elements on stains (136). Cultures are positive in only 50% of patients (274).

In kidney and heart transplant recipients, common manifestations of candidal infection include esophagitis, urinary tract infection, and intravenous line-related infections (106). Dissemination from these infected sites may occur. Colonization of the respiratory tract by *Candida* spp. is usually innocuous, even in the transplant recipient. However, following lung or heart/lung transplantation, involvement of the bronchial mucosa by *Candida* spp. may lead to rupture of the surgical anastomosis and fungal mediastinitis (56).

Liver transplantation strongly predisposes to candidal infection, and *Candida* spp. have been reported to cause as many as 30% of infections in these patients (285). Common sites of involvement are the abdomen and abdominal wound (195, 285). Invasive or disseminated disease carries a poor prognosis. One review of infection following liver transplantation shows a 77% mortality associated with invasive candidiasis (132).

Fungal infections are also common in pancreas recipients, with *Candida* spp. being the major pathogens (149). Wound and intra-abdominal infections are again frequently encountered, as are upper and lower urinary tract infections (106, 149, 194, 198). Involvement of the pancreatic allograft is a devastating complication of candidal infection and often leads to removal of the organ (149).

***Aspergillus* spp.** Infections due to *Aspergillus* spp., which typically occur in less than 6% of patients (27, 63, 101, 235), are less common among transplant recipients than are those due to *Candida* spp. and bacterial or viral pathogens. Aspergillosis,



however, is perhaps the most greatly feared of the infectious complications in this group, as mortality approaches 100% (52, 63, 190, 201). The pathogenesis of infection by this organism and underlying host immune system defects contribute to this alarmingly high mortality.

Neutrophils provide the major host defense against *Aspergillus* spp. (91), and therefore it is not surprising that BMT recipients are at high risk of infection. Other factors influencing the risk of aspergillosis in BMT patients include underlying disease, donor and recipient age, donor match, type of conditioning, prolonged granulocytopenia, and GVHD (30, 221). Among solid organ recipients, infection with *Aspergillus* spp. is associated with the intense immunosuppression used to treat rejection (101, 106, 133, 291).

Whereas immunosuppression is one prerequisite for invasive infection by *Aspergillus* spp., environmental exposure is another. Since *Aspergillus* spp. are ubiquitous soil-associated organisms, environmental exposure to aspergilli is common. Outbreaks of aspergillosis within hospitals have been associated with periods of construction (88, 187, 234). Sampling of hospital air has clearly shown a rise in spore counts during times of construction inside or outside the hospital, presumably due to agitation of dust and soil and hence an increasing concentration of airborne organisms. When inhaled by the appropriate host, this common organism may then establish infection.

Considering the pulmonary portal of entry, it is not surprising that the lungs are the predominant site of infection. Clinical findings of invasive pulmonary aspergillosis are nonspecific, and a high clinical suspicion is necessary to facilitate an early diagnosis. The organism demonstrates a tendency to invade and obstruct blood vessels, resulting in tissue infarction and necrosis. While fever, shortness of breath, and cough may be present (27, 155, 291, 306), symptoms associated with obstruction of blood supply may mimic those of pulmonary embolism and infarction, with pleuritic chest pain, hemoptysis, and pleural friction rub (155). The patient may also present with a fever that is unresponsive to antimicrobial agents and with no focal complaints (27, 155). Chest radiographs may show focal or diffuse infiltrates, nodules, cavities, or wedge-shaped infarcts or may be normal despite rapid clinical deterioration (27, 138, 155, 168, 291, 306). Computed tomography may provide early evidence of pulmonary parenchymal disease suggestive of aspergillosis when plain radiographs are normal or nonspecific (168). Compared with neutropenic BMT patients, solid organ recipients tend to have a more insidious onset of disease, with a paucity of objective pulmonary findings (63). Definitive diagnosis, made by identifying characteristic hyphal elements in a tissue biopsy specimen, is often not made until the infection is widely disseminated or is made only at the time of autopsy (56, 291).

Localized upper-airway involvement by *Aspergillus* spp. has previously been described in immunocompromised patients and is characterized by pseudomembrane formation and airway obstruction (23, 43, 111, 199). More recently, the new entity of invasive bronchial aspergillosis or ulcerative tracheobronchitis has been described in lung transplant recipients (129). Visualization by fiber-optic bronchoscopy reveals ulceration, necrosis, or pseudomembrane formation, and microscopic examination of biopsy specimens demonstrates the invasion of cartilage by hyphae (129). In this population, although *Aspergillus* spp. initially cause local invasion limited to the anastomotic site and large airways, there is potential for widespread dissemination. Patients with isolated tracheobronchial disease tend to fare better than those with invasive pulmonary aspergillosis.

Aspergillosis localized to the paranasal sinuses is seen in 15% of immunocompromised patients with this infection (165) and is most commonly seen in the neutropenic cancer patient. Although reported in the transplant population (241), it is an uncommon manifestation of disease in this group. In keeping with the pathophysiology of infection with *Aspergillus* spp., disease in the sinuses may become destructive, with involvement of the hard and soft palates, orbits, facial tissues, and base of the brain (27, 306). In addition to local involvement, the organism may disseminate hematogenously from the sinuses, resulting in multiple noncontiguous areas of involvement.

Dissemination of *Aspergillus* spp. from a primary pulmonary focus of the paranasal sinuses is frequent in the transplant patient, and when dissemination occurs, CNS involvement is commonly found (306). Meningitis, meningoencephalitis, hemorrhagic abscesses, and granulomatous involvement have been described (165, 306). In the brain, as elsewhere, the organism tends to involve vascular structures, with subsequent hemorrhage or infarction (27). Less common sites of infection with *Aspergillus* spp. include the skin (4, 81, 89), cardiovascular system (13, 229, 288), bone (5, 272), external ear (202), urinary tract (63), peritoneum (217), and thyroid gland (259, 306).

**Fusarium spp.** *Fusarium* spp. are becoming more commonly recognized as opportunistic pathogens of neutropenic patients. *Fusarium* spp. are common plant pathogens (179) and historically have been described as the causative agents of a toxin-mediated gastrointestinal illness, alimentary toxic aleukia, which often is associated with myelosuppression (151). In immunocompromised patients, they cause locally invasive or disseminated disease (7, 8, 85, 179, 214). The most prominent risk factor for infection with *Fusarium* spp. is neutropenia, and thus infection in the BMT patient can be expected. In this population, *Fusarium* spp. are second only to *Aspergillus* spp. as non-candidal fungal pathogens (170).

Clinical manifestations of infection reported in BMT patients include invasive sinus infection, cutaneous and soft tissue infection, fungemia, pulmonary infection, osteomyelitis, bone marrow involvement, and dissemination to multiple organs (25, 85, 152, 170, 175). The neutropenic patient with disseminated fusariosis typically presents with fever, myalgias, and skin lesions (85). The outcome is highly dependent upon the return of functioning neutrophils. The importance of the neutrophil in susceptibility to infection and outcome is borne out by the finding of this infection exclusively during the early posttransplantation neutropenic period (a median of 17 days following transplantation) and by recovery occurring only in patients with fairly rapid bone marrow reconstitution (85). The pathophysiology of infection with *Fusarium* spp. is similar to that of infection with *Aspergillus* spp., being characterized by invasion of blood vessels, resultant tissue necrosis, and widespread dissemination (8). The clinical appearance of skin or nasal mucosal lesions reflects this with the finding of black necrotic eschars (7, 8, 85), which are difficult to distinguish from those caused by other pathogens such as *Aspergillus* spp., *Pseudomonas* spp., or *Mucor* spp. *Fusarium* spp. differ from *Aspergillus* spp. in their frequent isolation from blood and more common association with skin lesions (7, 85, 214). The isolation of *Fusarium* spp. by typical surveillance culture methods, i.e., in sputum, stool, and nasal swabs, is of unclear significance if there are no concurrent clinical manifestations of infection (85).

**Cryptococcus neoformans.** A fungus that causes infection in both immunocompetent and immunocompromised patients is the ubiquitous *C. neoformans*. Cell-mediated immunity provides the most important host defense, and susceptibility to

infection with this common organism is dependent upon the immune system status. Cryptococcal infections tend to occur late in the posttransplantation period (224, 228). Given the relatively low level of immunosuppression at this stage of the transplantation process, the appearance of infection is thought to be due to new exposure rather than reactivation of a latent focus (294).

Although the portal of entry is pulmonary, clinical manifestations of pulmonary infection are uncommon (190, 240). The most common manifestation of infection following dissemination of the organism is subacute meningitis (240, 294). Another common extrapulmonary site of involvement is the skin, with various physical findings, including papules, nodules, plaques, ulcers, and cellulitis (42, 89, 106, 254).

As neutropenia is not a major risk factor for cryptococcal infection, it is not surprising that this infection is uncommon among BMT recipients. In a review of 1,186 BMT patients, no cryptococcal infections were reported (170). In another study of nosocomial pneumonia in BMT patients, there was one case of cryptococcal pneumonia among 275 patients (190).

**Mucormycoses.** The classical example of infection by the family *Mucoraceae* is rhinocerebral mucormycosis in the diabetic host. This form of infection is uncommon in transplant recipients. Sites of involvement in transplant recipients include the lungs, brain, kidney, bone, and sinonasal region (169, 166, 102, 170). The finding of noncontiguous sites of involvement suggests dissemination via the bloodstream, an uncommon finding in the diabetic host. In two large series of BMT patients with infection, mucormycosis was found in less than 1% (169, 170). Disease occurred in both neutropenic and nonneutropenic hosts throughout the posttransplantation period. Mortality was high, although limited sinonasal disease may have a better prognosis, as it may be amenable to surgical debridement.

**Endemic mycoses.** Organ recipients living in areas of endemic histoplasmosis, coccidioidomycosis, and blastomycosis infections are at risk of primary infection following immunosuppression. Other recipients may experience reactivation of a latent infection acquired during a distant exposure. *Histoplasma capsulatum*, found in the Mississippi and Ohio river valleys, is the most frequently encountered pathogen in this group. It tends to be disseminated at the time of diagnosis and may have a rapidly progressive or chronic, indolent clinical course (89, 125, 296). Nonspecific symptoms of fever, malaise, and sweats, with or without signs of pulmonary involvement, are common (79, 296). Evidence of dissemination, such as bone marrow suppression, intestinal obstruction, meningitis, or diffuse skin lesions, may be prominent. An increasing incidence among transplant recipients has been shown to reflect regional outbreaks (296). Although it may be seen at any time, histoplasmosis tends to occur in the late posttransplantation period, with an average time of onset greater than 1 year following transplantation (58). This may support the contention that primary exposure, rather than reactivation, is the main mode of acquisition (296). *H. capsulatum* is also one of the organisms documented to be transmitted by an infected allograft (113).

Although coccidioidomycosis is uncommon in transplant patients, infection, when found, is also usually disseminated. *Coccidioides immitis* is found in the arid and semiarid areas of North, Central, and South America described as the Lower Sonoran Life Zone. Infection tends to occur earlier in the posttransplantation course than does histoplasmosis, suggesting reactivation as the most likely form of initiation (45, 294). Dissemination occurs in most immunocompromised patients, with involvement of skin, bone, CNS, liver, and kidneys (45, 79, 89, 106, 294). Pulmonary involvement, uncommon in some

immunocompromised groups such as human immunodeficiency virus (HIV)-infected patients, is more common in transplant patients (45). This infection carries a very poor prognosis, with mortality exceeding 60% (45, 89). In patients treated for coccidioidomycosis prior to transplantation, fatal reactivation has occurred, questioning the feasibility of transplantation in these patients and suggesting the need for prophylactic therapy in high-risk patients (45, 215, 239).

*Blastomyces dermatitidis*, found in the southeastern and south central United States, is the least common of the endemic mycoses found in the transplant population. A recent review cites only five cases reported in the literature (245). These cases occurred throughout the posttransplantation period, ranging from 3 weeks to 4 years. They were not associated with any specific form of immunosuppression. Infection most often involved dissemination from a pulmonary source. Mediastinal adenopathy, skin lesions, and subretinal lesions were reported.

***Pneumocystis carinii*.** As a cause of subacute pneumonia in the transplant recipient, *Pneumocystis carinii* is seen in the early and mid posttransplantation periods, and it is also seen in the later period if the patient is experiencing rejection or CMV infection (82). Infection is more common and more severe in lung transplant recipients, perhaps due to impaired local defense mechanisms in addition to general immunosuppression (99). It has also been suggested that *P. carinii* infection may predispose the lung transplant recipient to chronic rejection (99).

*Pneumocystis* pneumonia is typically a diffuse interstitial process, and the patient presents with fever, malaise, hypoxia, and nonproductive cough. It may be difficult to differentiate from pulmonary involvement by other opportunists, and simultaneous infection with multiple pathogens is common (82). Clinically significant extrapulmonary involvement is uncommon (82).

## Parasites

***Toxoplasma gondii*.** *Toxoplasma gondii* is an obligate intracellular protozoan that commonly causes asymptomatic infection in immunocompetent individuals but has the ability to cause life-threatening infection in immunocompromised patients. The organism remains dormant in the body following primary infection and is capable of future reactivation during times of immune system deficiency. Positive pretransplant serologic tests identify the patients at risk of reactivation disease. Common clinical sequelae of reactivation include involvement of the CNS, with encephalopathy, meningoencephalitis, and cerebral mass lesions (230). Symptoms of CNS infection include both focal and nonfocal deficits such as hemiparesis, seizures, and altered mental status. Pneumonitis and myocarditis are also reported (303).

In addition to reactivation of an organism dormant in the host, a problem unique to the transplant patient is the ability of the organism to be present in the allograft, with primary infection occurring at the time of transplantation. Primary toxoplasmosis appears to be more severe than reactivation disease (86) and occurs much earlier following transplantation, often within the first month (302). Among organ recipients, the seronegative cardiac transplant recipient is at greatest risk for acquisition of the organism from an infected donor heart (260). The most common form of disease in this situation is myocarditis (86), with possible dissemination and multiorgan involvement (146). Definitive diagnosis requires tissue biopsy with the demonstration of the organism histologically.

Among BMT patients, toxoplasmosis is rare, occurring in

only 12 of 3,803 allogeneic bone marrow recipients and none of 509 autologous recipients in one review (257). The median time to clinical presentation in this series was 59 days following transplantation, although some cases occurred in the late post-transplantation period. Evidence of infection in the early neutropenic period is described as well (65). The diagnosis was made prior to death in only 16% of patients, with the most common sites of involvement being the brain followed by the heart and lungs. All patients were seropositive for the organism pretransplantation, and all had severe GVHD.

***Strongyloides stercoralis*.** The intestinal nematode *Strongyloides stercoralis* is found in many parts of the world, including the southern United States. After initial infection, the organism can survive in the asymptomatic host for many years. Tissue invasion appears to be prevented by a normal cell-mediated immune response (210). Following transplantation, the host who harbors this organism is at risk for a severe form of autoinfection—the hyperinfection syndrome. This syndrome is characterized by enhanced reproduction, tissue invasion, and dissemination of larvae to multiple organ systems. As the parasite passes through the intestine, it is thought that bacteria are carried along with the parasite, with the potential for spread to distant sites. Symptoms include fever; gastrointestinal complaints associated with ulcerative, hemorrhagic colitis; pulmonary manifestations of cough, wheezing, hemoptysis, and infiltrates; and enteric gram-negative bacteremia, peritonitis, and meningitis. A maculopapular or urticarial rash may be present on the trunk and lower extremities (66, 89). Eosinophilia may or may not occur. Infection typically becomes evident within the first 3 months following transplantation (167) but has been documented several years into the posttransplant course (66).

***Leishmania* spp.** Infections caused by the intracellular protozoan *Leishmania* spp. are usually transmitted by the bite of the sand fly, but the organism has also been transmitted by blood transfusion and possibly by organ transplantation (116). *Leishmania* spp. are widely distributed in the world, with different species endemic to different areas. In the United States, *Leishmania mexicana* has been found in Texas (87, 92, 100). Manifestations of infection are classified as cutaneous, mucocutaneous, and visceral. The type of infection is dependent upon the infecting species. Like *S. stercoralis*, *Leishmania* spp. cause asymptomatic infection and then remain dormant in the host for many years, becoming clinically apparent during periods of immunosuppression (17, 171). Cell-mediated immunity provides the major host defense against active infection, and transplant patients with a history of travel to an area of endemic infection are at risk for reactivation of the organism following the imposition of immunosuppression.

Visceral leishmaniasis (kala-azar) is characterized by fever, hepatosplenomegaly, lymphadenopathy, and pancytopenia and is seen in the Mediterranean region and Latin America (116, 168, 207). Cutaneous disease is characterized by single or multiple ulcerating papular lesions on areas of exposed skin at the sites of sand fly bites; it is seen in the Middle East, Mexico, Central America, South America, and Texas (89, 92). Leishmaniasis is often diagnosed by histopathologic detection of amastigotes in bone marrow aspirates or skin biopsy material, and techniques for in vitro cultivation of promastigotes, although not widely available, may be attempted (82). Mucocutaneous leishmaniasis, a necrotizing, destructive process involving the oral and nasal mucosa, is a long-term complication of cutaneous disease (82). It has been suggested that pretransplantation serologic testing may be useful in areas of endemic infection to identify individuals who may harbor the organism, so that treatment may be provided prior to immunosuppression (171).

Despite treatment, disseminated disease is often relapsing or fulminant in immunocompromised patients (80, 171, 280).

***Trypanosoma cruzi*.** Chagas' disease (American trypanosomiasis) is caused by the protozoan hemoflagellate *Trypanosoma cruzi*. It is transmitted by the bite of a triatomid insect, transplantally, or by blood transfusion or transplantation of an infected organ. Primary infection is often asymptomatic, and the organism then remains dormant within the host. *T. cruzi* is endemic in Mexico and Central and South America and has been found in the blood supply in the United States as well. As many as 80% of persons living in regions of endemic infection are estimated to be infected (137). The presence of antibodies to the organism is indicative of prior exposure and thus risk of reactivation disease. Currently available tests have low specificity, however, and the antibody response is often impaired following institution of immunosuppression.

Acute disease may be asymptomatic or may have a variety of manifestations, including fever, myalgias, lymphadenopathy, and hepatosplenomegaly. Meningoencephalitis and myocarditis are less common. A minority of patients will develop chronic disease, which is characterized by cardiomyopathy and the gastrointestinal "mega" syndromes—megaesophagus and megacolon. The heart is commonly involved in the chronic stage of illness, and symptoms include arrhythmias, congestive failure, and thromboembolism.

The characteristics of asymptomatic primary infection and latency make this disease a concern for the immunocompromised transplant patient with a history of travel to or residence in an area of endemic infection. Reactivation of *T. cruzi* in kidney transplant recipients with underlying chronic infection has been reported (164) but appears to be rare (60, 145). In contrast, a number of patients with Chagas' cardiac disease have been transplanted, and reactivation of disease is common in the allograft (26, 265). This parasite is a major cause of heart disease in areas of endemic infection and results in a progressive heart failure which leads to death. This population would therefore potentially benefit from cardiac transplantation. The clinical manifestations of reactivation differ somewhat from those observed in immunocompetent individuals and include fever, skin lesions, and myocarditis (265). The diagnosis is made by identification of the organism in skin or myocardial biopsy samples. These patients appear to respond well to treatment, and it is thought that transplantation is a viable option for patients with heart disease due to Chagas' disease (137, 265). Long-term follow-up will be important in determining the effect of the infection on allograft function. In addition to reactivation of latent disease within the recipient, the organism may be transmitted by blood transfusion or by the allograft (144, 283). Whether serologic evidence of disease should exclude a donor is unclear.

***Sarcoptes scabiei*.** A severe form of scabies caused by *Sarcoptes scabiei*, called Norwegian or crusted scabies, is seen in debilitated or immunocompromised patients. This parasite burrows into human skin to reproduce and lay eggs. It may be transmitted from person to person by casual contact. Cutaneous findings include widely distributed psoriasis-like hyperkeratotic crusted nodules and plaques, which may be only minimally pruritic. The nails, palms, and soles are frequently involved. Eosinophilia may be prominent. The immunocompromised host tends to have a much greater parasite burden than the competent host and therefore has more extensive skin involvement with these impressive skin findings. This form of infection has most recently been described in association with AIDS (103) and also been found in the transplant recipient population (77, 307). Diagnosis is made by identifying the organism in skin scrapings.



## Viral Agents

**Herpesviruses.** The human herpesvirus group comprises the major viral pathogens in both solid organ and BMT recipients. These include HSV-1, HSV-2, CMV, VZV, Epstein-Barr virus (EBV), and human herpesvirus 6 (HHV-6). Herpesviruses are common viruses to which a large proportion of the population is exposed early in life. These organisms may also be transmitted by an organ allograft (72). As latent viruses, their viral genome remains within infected cells for the life of the host, with the propensity for reactivation and expression during periods of immunosuppression. The potential oncogenicity of these viruses may be particularly pertinent to the transplant patient, who may be at risk for induction of uncontrolled cellular proliferation when normal immune surveillance mechanisms are impaired. Due to the inability of the humoral immune system to defend against these cell-associated viruses, the major host defense mechanism is the cell-mediated, virus-specific cytotoxic T cell (225).

Reactivation of HSV occurs early in the posttransplantation period in both solid organ and BMT patients, often within the first 2 to 3 weeks (Table 1) (30, 225). It also may reappear later if there are periods of intense immunosuppression. The most common manifestation of disease is labial and oral ulceration, which may be quite severe. Esophageal, genital, anal, and buttock involvement is also seen. Pulmonary involvement is uncommon in most solid organ recipients, and positive cultures from the lower respiratory tract may be difficult to interpret due to the high frequency of oral lesions as well as asymptomatic oral shedding with subsequent contamination of lower respiratory tract specimens. Airways traumatized by intubation or invasion by other pathogens, however, may become secondarily infected by HSV (225). In lung recipients, HSV pneumonia can be a more formidable entity (225), because impairment of local defenses may increase host susceptibility to this pathogen. HSV pneumonia also seems to be a more prominent problem among BMT patients (30).

CMV is one of the most common agents complicating transplantation, and infection typically occurs in the second through fourth months following solid organ transplantation and between engraftment and day 100 in BMT recipients (Table 1). The major factor in determining the risk of CMV infection in solid organ recipients is the pretransplant recipient and donor antibody status (107). Recipients who are seronegative and receive an organ from a seropositive donor are at the greatest risk of serious infection, because they may acquire primary infection from the allograft. Recipients who are seropositive prior to transplantation are also at risk of infection, but infection in this group is usually caused by reactivation of their latent virus and is typically less severe than primary infection. The seropositive patient may also experience superinfection by acquisition of a new strain from the allograft, the environment, or infected blood products. Seronegative recipients with seronegative donors may also acquire primary infection from exogenous sources. In contrast, among BMT recipients, although transmission of the virus to a seronegative recipient by the marrow of a seropositive donor may occur (160), donor CMV status seems to be of less importance since the virus apparently is not as easily transmitted by donor marrow as by a solid organ. Donor positivity may actually have a protective effect (97). The most common setting for CMV disease in BMT recipients is in seropositive recipients who experience viral reactivation of their endogenous strain (157, 160, 162, 300). The transmission of the virus by blood products (160, 162) probably plays a more significant role in BMT recipients in

comparison to solid organ recipients due to the increased requirement for transfusion in these patients.

The second most important determinant of the risk of CMV infection is the type of immunosuppressive regimen administered. The use of steroids has a minimal effect on viral reactivation (223), and the infrequency of CMV infection in other patient populations treated solely with steroid-containing regimens is notable. While cyclosporine- and FK506-based regimens also have little effect on viral reactivation, they may promote viral replication following reactivation (108, 223, 225). The agents capable of inducing reactivation are the monoclonal and polyclonal antilymphocyte antibody preparations such as antithymocyte globulin (39) and OKT3 (157, 206, 225). The marked suppression of the cell-mediated immune response with the elimination of circulating T cells by these agents is likely to be responsible for this finding. The incidence of CMV infection among patients receiving cyclosporine-based regimens is approximately 20%, while the incidence among those who also receive OKT3 may approach 60% (108). Other risk factors for CMV reactivation identified in BMT patients include the use of total body irradiation as a conditioning regimen and the occurrence of acute GVHD (30, 157, 158, 160, 162, 310).

The consequences of primary infection or reactivation of CMV range from asymptomatic viral shedding to life-threatening multiorgan involvement. The patient may present with a subacute mononucleosis-type syndrome which may be self-limited or which may progress to involve single or multiple organs with pneumonia, hepatitis, pancreatitis, esophagitis, gastritis, colitis, encephalitis, transverse myelitis, or skin lesions as clinical findings (89, 200, 223, 224, 225). CMV chorioretinitis, a common manifestation of infection in the HIV-infected patient, is seen infrequently in transplant recipients and occurs later in the posttransplantation course than the other manifestations of CMV infection—typically more than 6 months following transplantation (107).

While the clinical manifestations of infection can be devastating for the transplant patient, so are the indirect effects of infection with this virus. CMV is an immunomodulating virus and acts to suppress the host immune system (107). Leukocyte number and function are affected, and impairment of cell-mediated immunity is characterized by the inversion of the normal cytotoxic/suppressor cell ratio (140, 225, 237). This additional immunosuppression leads to a risk of superinfection with opportunistic bacteria and fungi (38, 107, 211, 223, 225, 226, 268). An increased incidence of *P. carinii* pneumonia among transplant recipients infected with CMV may be related to the suppression of alveolar macrophage function by the virus (78, 107, 186, 225, 226). This added burden to the immune system clearly compounds the morbidity and mortality caused by the virus. Other important indirect effects of the immunomodulation imposed by CMV infection is immune system-mediated damage to the allograft and allograft rejection.

The relationship between CMV infection and allograft dysfunction was first described in renal transplant recipients (84, 223, 225, 250). A distinctive glomerular lesion has been found in the renal allografts of patients with CMV viremia, the etiology of which may involve the change in T-cell subsets induced by the virus (173, 225). CMV infection has also been purported to cause indirect damage to liver allografts and is possibly associated with the vanishing bile duct syndrome (184, 196). CMV has been linked to both acute rejection and accelerated graft arteriosclerosis in heart transplant recipients (96, 142, 292). It may also be indirectly involved in the pathogenesis of pulmonary allograft rejection and bronchiolitis obliterans in lung and heart-lung recipients (126).



Finally, as with the other herpesviruses, there is interest in the role that CMV may play in oncogenesis. As latent transforming viruses, members of the herpesvirus group may induce uncontrolled cellular proliferation under circumstances of immunosuppression. Although this potential exists, there is as yet no convincing evidence implicating CMV in the pathogenesis of malignancy in the transplant population, unlike what is known regarding EBV.

The diagnosis of CMV disease is challenging due to the myriad of clinical presentations and inherent difficulty in the interpretation of culture and serologic data. This common latent virus can often be detected, but the significance of such detection is often unclear. Common associated findings include leukopenia with the presence of atypical lymphocytes, thrombocytopenia, elevation of transaminase levels, and unexplained fever. Disease due to CMV is best confirmed by the detection of characteristic cell changes and CMV inclusions on histologic examination of tissue. One of the greatest challenges to clinical microbiologists in the arena of transplant medicine is in the development of methods to detect clinically significant CMV infection in a timely, sensitive, and cost-effective manner (see below).

While VZV infection occurs in approximately 10% of solid organ recipients and tends to be a self-limited disease (225), it occurs in up to 40% of BMT recipients and is associated with a mortality rate of over 30% in untreated patients (30). In both groups, infection occurs more than 2 months following transplantation and may pose a threat for several months or years. In the BMT patient, risk factors include allogeneic transplantation and acute or chronic GVHD (30). Manifestations include typical single or multiple dermatomal zoster and disseminated infection with visceral involvement such as hepatitis, encephalitis, and hemorrhagic pneumonia (30, 225).

EBV is an extremely common latent herpesvirus, and over 90% of the adult population harbors the virus. The virus remains latent within B cells, and viral reactivation may occur during periods of immunosuppression. The latency of EBV is unstable, and viral replication and excretion can at times be identified even in the normal host, unlike the latency of CMV, which is very stable with reactivation possible only in the setting of marked immunosuppression (224). Given the high rate of latent infection in the population, infection in the transplant recipient is usually due to reactivation, but it may be acquired from the donor organ or blood products. In the normal host, latent EBV is prevented from proliferating by the immune system surveillance of major histocompatibility complex-restricted, EBV-specific cytotoxic T cells (225, 269). Under the influence of immunosuppressive medications, however, these EBV-infected B cells may be allowed to proliferate.

There is a wide spectrum of clinical illness attributed to EBV infection and reactivation. Clinical manifestations of EBV infection are often difficult to distinguish from those of CMV. They include a nonspecific mononucleosis syndrome; hepatic, gastrointestinal, pulmonary, or neurologic involvement; and allograft dysfunction (224, 225). When lymphoid proliferation is unchecked, posttransplantation lymphoproliferative disorder (PTLD), a long-recognized complication of immunosuppression, may result. Disease may be fairly benign and polyclonal or aggressive with monoclonal tumor growth. Although it may occur many years following transplantation, PTLD is most common in the first posttransplantation year (20, 188). The incidence is lowest in renal transplant recipients and highest in heart-lung recipients (46). Risk factors include the use of antilymphocyte antibodies (20, 188), OKT3 (287, 271), CMV disease (20), and perhaps a high cumulative level of immunosuppression (20). A study of nonrenal solid organ recipients

suggests a synergistic effect between pretransplantation EBV seronegativity, OKT3 use, and CMV seromismatch on the risk of PTLD (271). Depletion of T cells in the bone marrow and HLA mismatching place the BMT recipient at greater risk for PTLD (246). Extranodal disease is more common than nodal disease in transplant patients (20, 224, 225), with the gastrointestinal tract and CNS being the most common sites of involvement (20). The allograft is involved in as many as 18% of patients (197), and the presence of PTLD should be considered in the patient with unexplained allograft dysfunction (20). High levels of EBV replication and shedding appear to precede overt disease (224, 225), and the finding of positive cultures may be significant in the evaluation of the patient with risk factors for PTLD and an appropriate clinical presentation (224, 225).

HHV-6 is a recently described member of the herpesvirus family and appears to be a latent virus that is prevalent in the community. Most adults show serologic evidence of previous exposure. It has been associated with exanthem subitum in children and is probably one of the viral causes of a mononucleosis syndrome in adults (3, 189) and possibly a cause of hepatitis (71). As a latent virus, the potential for HHV-6 to reactivate during periods of immunosuppression and cause disease has been explored. Its role in posttransplant infections, however, has yet to be completely elucidated. Among BMT patients, HHV-6 has been linked to interstitial pneumonitis (34, 48), bone marrow suppression (69, 128), encephalitis (70), and rash (305). HHV-6 has been shown to reactivate in solid organ recipients as well, but the clinical consequences of such reactivation are unclear (186, 304). The tropism of the virus for lymphocytes and macrophages (1, 128) is interesting and may lead to speculation about the role of this virus in the pathogenesis of posttransplant lymphoreticular malignancy. As with all latent viruses, laboratory diagnosis can be difficult in the immunocompromised patient due to inconsistent antibody production. An additional diagnostic problem is the partial homology between HHV-6 and CMV and thus a potential for cross-reactivity (73, 225, 270).

**Hepatitis viruses.** Although the above members of the herpesvirus family are associated with liver disease, the typical hepatitis viruses are more common causes of acute and chronic hepatitis in the transplant population. Hepatitis B and C viruses (HBV and HCV) are the agents that most often result in chronic hepatitis and can cause significant morbidity and mortality in the immunosuppressed transplant recipient. A reactivation or exacerbation of preexisting chronic disease may occur following immunosuppression, or the patient may acquire the viruses from the allograft or transfusion of blood products.

The consequences of immunosuppression in a patient with preexisting HBV infection can be devastating. Immunosuppressive agents, steroids in particular, appear to stimulate viral growth (224, 225). Even a patient with minor or stable liver disease prior to transplantation may develop rapidly progressive HBV disease following initiation of immunosuppression. Chronic progressive hepatitis, chronic active hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma may all occur in this group (124, 212). Liver transplant recipients are notable for their adverse outcome when the disease in the native liver is due to HBV. In these patients, the virus recurs in the allograft and may cause rapidly fulminant disease and a high rate of graft loss (62, 185). A unique hepatic lesion has been described in hepatic allografts infected with HBV and is described as fibrosing cholestatic hepatitis (57). In other transplant recipients, HBV infection is more likely to have long-term effects, with adverse clinical outcome due to the above manifestations of chronic infection as well as an increased risk

of infection with other opportunists due to the immunomodulating effects of chronic viral infection (147, 192, 213).

The most common cause of chronic liver disease following transplantation is HCV (40, 124). The virus may be present in the recipient prior to transplantation or may be transmitted by the allograft or by transfusion of blood products. Serologic studies to detect evidence of HCV lack 100% sensitivity, which accounts for the inadvertent transplantation of a positive organ or transfusion of blood products harboring the virus. Disease tends to be more slowly progressive than that due to HBV, with manifestations beginning 2 years or more following transplantation (124, 213). Hepatocellular carcinoma may also be a consequence of HCV infection (308).

**Human immunodeficiency virus.** Transplantation of an organ from an HIV-positive donor has dire consequences for the recipient, with close to a 100% risk of transmission and resultant HIV infection, which tends to progress more rapidly than in other groups (76, 225, 227). With the uniform screening of donors and exclusion of donors with risk factors for HIV infection, this problem has largely been eliminated. It has been suggested that PCR or viral culture methods may be used to identify infection in high-risk donors who may have recently acquired the virus but have not yet produced antibodies (227, 251). As false-negative HIV testing has also been attributed to dilution secondary to massive transfusion of donors (36), as seen in some trauma victims, it is recommended that HIV testing be performed on a pretransfusion blood sample in such a situation (193).

Organ transplantation in HIV-infected patients has been discouraged (225). Certain patients, however, when transplanted prior to severe immunocompromise appear to do fairly well and may survive for several years with a functioning allograft (76, 225, 227, 281). Each case should be considered on an individual basis, with careful consideration given to the limitations of organ availability.

**Respiratory syncytial virus.** Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infection in children in the winter and spring months, and in normal adults it is most commonly associated with a mild upper respiratory illness. RSV has, however, been reported as a serious cause of pneumonia in elderly and immunocompromised persons (75, 209). RSV infection has been reported in solid organ recipients (75, 256), but appears to be a more common and significant pathogen among BMT patients (75, 104, 105).

Interstitial pneumonitis is a major complication of BMT, with CMV being the most common pathogen. RSV has also been identified as a cause of posttransplantation pneumonia in this population (75, 104, 105), with a mortality rate exceeding 50%. Infection has been reported throughout the posttransplantation period, from the early preengraftment stage to 1 year or more following transplantation. Manifestations of infection range from mild upper respiratory tract disease to fulminant pneumonia. A typical clinical course consists of upper respiratory symptoms preceding lower tract involvement and respiratory failure. Bilateral interstitial infiltrates are the most commonly reported radiographic abnormality, but localized, lobar infiltrates may be seen as well.

Early diagnosis and treatment of RSV in the BMT patient appears to favorably affect the outcome (75, 104, 105). While definitive diagnosis is established by culture, antigen detection from bronchoalveolar lavage (BAL) specimens by either immunofluorescent antibody assay (IFA) or enzyme-linked immunosorbent assay (ELISA) may be extremely helpful in providing early evidence of infection (75, 104, 105). The potential for nosocomial spread of this virus also emphasizes the importance of early diagnosis.

**Adenoviruses.** The adenoviruses are nonenveloped DNA viruses with the potential for latency. They are common causes of minor infection in the general population but can cause serious, life-threatening infection in immunocompromised persons (109). Adenovirus infection has been documented in both solid organ and BMT patients. Acquisition of infection appears to be due to reactivation, primary infection, or even transmission by the allograft (83, 176, 248).

The most common manifestation of infection in renal transplant recipients is acute hemorrhagic cystitis, and infection tends to be localized to the urinary tract (33, 109). In the liver recipient, hepatitis is seen most frequently and is often associated with disseminated disease (109, 161). Adenovirus disease is likewise often disseminated in the BMT population, in which it carries a 60% mortality rate (109). Infection may involve the lungs, liver, CNS, gastrointestinal tract, or urinary tract (59, 83, 109, 248). Although hemorrhagic cystitis is often attributed to the use of cyclophosphamide in the BMT patient, recognition that hemorrhagic cystitis may have a viral origin is important in this population (6, 83, 163, 248). Adenovirus has also been implicated as a cause of virus-associated hemophagocytic syndrome following BMT (135). GVHD appears to be a risk factor for adenovirus infection (83, 248).

## ROLE OF THE CLINICAL MICROBIOLOGY LABORATORY

### Extent of Services

As the previous discussion on infections in the transplant patient would suggest, the clinical microbiology laboratory plays a vital role in assisting the physician in the medical management of this patient population. Prior to establishing a transplantation service in a specific institution, the microbiology laboratory should be consulted about the extent of services provided to its clients and customers. The laboratory should review its standard operating policies and methods of procedure to ensure that it can meet the needs of this select patient population. To a certain extent, the type of transplantation procedure performed will dictate the laboratory services needed. In general, however, laboratories must be prepared to offer expert services in bacteriology, mycology, parasitology, virology, and serology (18). If outside reference laboratories are to be used for any tests related to transplant patients, they must ensure to provide the short turnaround times often needed because of the emergent nature of the surgical procedure, as well as the necessity for the timely diagnosis of infection in the posttransplantation period.

If resources allow, the laboratory should consider providing dedicated space and personnel for performance of microbiology services for transplant patients. Communication with physicians regarding the status of patient cultures is paramount. In the authors' institution, laboratory personnel meet each morning with members of the infectious disease team who are monitoring patients on the transplantation service. These meetings provide the team with the most current status of all cultures and allow for an exchange of information to assist the laboratory in providing the most clinically relevant, cost-effective workup of specimens. The meetings also serve as a forum for continuing education and allow laboratory personnel to more directly appreciate how their efforts affect patient care.

### Pretransplant Evaluation

The presence of active infection in a prospective transplant recipient is often a contraindication to clinical transplantation,

TABLE 2. Pretransplantation screening

Allograft recipient
Microbiological evaluation of any active pre-existing infection
Serologic testing for CMV, HSV, EBV, VZV, HBV, HCV, HIV, and <i>T. gondii</i>
Ova and parasite examination for <i>S. stercoralis</i>
Allograft donor
Serologic testing for CMV, HBV, HCV, and <i>T. gondii</i>
Microbiologic evaluation of potential sources of active or dormant infection with dimorphic fungi or <i>M. tuberculosis</i> <sup>a</sup>
Culturing of cadaveric organs
Culturing of organ perfusates and transport media

<sup>a</sup> If exposure history suggests risk.

and so physicians rely on the routine diagnostic services provided by the clinical microbiology laboratory to identify the etiologic agents of preexisting infection in the pretransplant patient. It is important to recognize that as expertise in transplantation grows, an increasing number of patients with severe underlying illnesses will become eligible for these procedures. Therefore, an increasing proportion of patients presenting with acute bacterial infections prior to transplantation is likely to be seen. Examples include aspiration pneumonia in the patient with advanced hepatic encephalopathy, line sepsis in the renal dialysis patient, and respiratory infection in the chronically intubated patient with end-stage pulmonary disease. It is incumbent upon the laboratory to provide the timely processing of specimens such as blood, body fluids, respiratory secretions, and catheter tips and, when appropriate, to provide rapid information on the results of Gram stains and cultures. The length of hospitalization prior to transplantation is pertinent, as the hospitalized patients' endogenous flora will be replaced by more resistant gram-negative organisms and resistant staphylococci shortly after entry into the hospital. If the patient has already experienced a prolonged hospitalization, prior microbiological data can be of great help in identifying organisms that have been encountered previously and that may continue to cause problems. Likewise, knowledge of antibiotic resistance patterns of nosocomial organisms through laboratory-generated antibiograms is important to the clinician in foreseeing which bacteria may be particularly troublesome.

Serologic screening of the recipient and donor for a variety of infectious processes is an important part of the pretransplantation evaluation (Table 2). These studies are commonly used for the detection of active or latent infection with the herpesvirus family (HSV, CMV, EBV, and VZV), as well as HBV, HCV, and HIV. Knowledge of the pretransplantation viral serologic status is important in a number of respects. The recipient's pretransplant CMV serologic status, for example, will often determine whether CMV-negative blood products should be given in the perioperative and immediate postoperative period or whether antiviral chemoprophylaxis is indicated (153, 154), and in some cases, it will determine the serologic status of the organ donor (2). Similarly, the transplant recipient who is seronegative for EBV is at increased risk for a serious EBV infection or EBV-mediated PTLTD if given an organ or bone marrow graft from seropositive donor (112, 312). While no specific prophylactic measures or antiviral therapies are yet available, the knowledge of the recipient's pretransplantation EBV serostatus can be helpful in the subsequent evaluation of the symptomatic patient (286).

As mentioned previously, HSV and VZV infections in the transplant patient usually represent reactivation disease and are self-limited or respond quickly to treatment. In BMT re-

ipients, a high serologic titer pretransplantation is predictive of reactivation of HSV but not VZV (290). Occasionally, these agents manifest as primary infections in the seronegative recipient, either de novo or by carriage in the transplanted allograft (72). Transplant recipients who are seronegative for VZV are at risk of severe primary varicella infection if they contract primary VZV infection from an individual with active viral shedding. Pretransplantation evaluation revealing VZV seronegativity should thus prompt a consideration of vaccination prior to transplantation. Lastly, the presence of multiple positive serologic tests for the herpesviruses in either the BMT recipient or donor increases the chance of developing GVHD (28), and this information may aid the clinician in the post-transplantation period.

In heart and heart-lung transplantation, the serologic status for infection with *T. gondii* in both the donor and recipient should also be determined prior to transplantation. The risk of acquisition of the organism from the allograft can be identified by a lack of *Toxoplasma* antibodies in the recipient and the presence of antibodies in the donor. Among such "mismatches," studies have indicated that more than 50% of recipients may develop primary infection (260, 302). Seronegative recipients who receive organs from seropositive donors receive prophylactic treatment for toxoplasmosis.

Rarely, dormant fungal or mycobacterial infection in the donated organ is passed on to the recipient, with devastating results (225). Thus, it is important in the evaluation of a living donor that a careful clinical and epidemiological history be obtained and, when necessary, that tuberculin skin testing and fungal serologic testing be performed.

As strongyloidiasis is a devastating complication of immunosuppression, with over 50% mortality (66, 167), careful evaluation of patients at any risk of exposure is essential. Stool specimens as well sputum, urine, and duodenal aspirates may be examined for characteristic organisms. It has been suggested that stool examination become part of the pretransplantation workup in all patients, with a more extensive evaluation in patients with a history of travel to or residence in an area of endemic infection (66, 167).

To prevent the transplantation of infected organs and tissues, cultures may be sent to the laboratory immediately prior to organ procurement. In kidney donors, for example, urine samples may be obtained directly from the ureters and submitted for culture and Gram stain. Additional safeguards against the transplantation of infected or contaminated organs include the culturing of organ perfusates or transport media (225).

#### Evaluation of the Transplant Recipient with Suspected Infection

The causes of infection in the transplant patient are variable and very much dependent on the type of transplantation procedure performed and the time of occurrence during the post-transplantation course. When the transplanted organ itself is involved, the differential diagnosis often includes both infection and allograft rejection, and the clinician relies upon the clinical microbiology laboratory to help rule out infection. The diagnosis of graft rejection at times is made only after exclusion of infection (286). Thus, it is imperative to have a standardized approach to the microbiological evaluation of the transplant patient with suspected infection.

Specimens to be collected for detecting various pathogens in the transplant recipient with suspected infection are listed in Table 3. When fever alone or other nonlocalizing signs occur, blood and urine for bacterial, fungal, and viral culture should be collected. The use of at least two 10-ml samples of blood,



TABLE 3. Microbiological evaluation of the transplant patient with suspected infection

Specimen	Microscopic examination <sup>a</sup>			Cultures <sup>a</sup>					Other tests or cultures that may be considered
	Gram stain	Kinyoun's stain	Calcofluor white stain	Routine aerobic	Anaerobic	Acid fast	Fungal	Viral	
Blood				X	X	X	X	X	Cryptococcal antigen test, CMV antigenemia assay
Urine	X	X		X		X	X	X	<i>Legionella</i> antigen assay
Sputum	X	X	X	X		X	X	X	
BAL or brush biopsy	X	X	X	X	X <sup>b</sup>	X	X	X	<i>Legionella</i> DFA and culture, <i>Mycoplasma</i> culture, PCP exam, RSV IFA or ELISA
Wound	X	X	X	X	X	X	X		
Lesion	X	X	X	X		X	X	X	HSV antigen ELISA
Tissue or body fluids	X	X	X	X	X	X	X	X	
Cerebrospinal fluid	X	X		X		X	X	X	Cryptococcal antigen test, India Ink exam
Intravenous catheter tip				X <sup>c</sup>					
Stool				X					Ova and parasite exam, <i>Clostridium difficile</i> toxin assay

<sup>a</sup> Boldface type indicates that the examination is routinely performed.

<sup>b</sup> Protected specimen brush only.

<sup>c</sup> Roll-plate method.

collected from two separate veins or from the same vein with an interval of 30 min to 1 h, will reliably detect most episodes of bacteremia (32). In the absence of a urinary catheter, a freshly voided midstream specimen of urine is obtained for microscopic evaluation and quantitative culture. A pure culture of  $>10^4$  CFU/ml may represent significant bacteriuria, especially if the patient is receiving prophylactic antibiotic therapy (68). The standard criteria (44) for significant bacteriuria should be applied to any sample of urine collected via a catheter.

For the patient with a suspected wound or soft tissue infection, it is always preferable to collect tissue samples, but if this proves impractical, swab samples of pus or exudate or aspirates of deep abscesses may be collected. Specimens should be partitioned into appropriate collection devices for aerobic and anaerobic culture and transported quickly to the laboratory. At a minimum, tissue specimens are processed for histologic examination, Gram stain, and routine aerobic and anaerobic culture. A more comprehensive evaluation includes special stains and cultures for mycobacteria, *Nocardia* spp., and fungi.

Sputum for Gram stain and culture should be collected from all patients with pulmonary complaints or abnormalities seen on chest roentgenograms. Expecterated sputum can reveal the cause of up to 75% of bacterial pneumonias in transplant patients (119), although colonization of the oropharynx with gram-negative bacilli can be misleading. Laboratories should use caution when applying sputum screening criteria based on the relative numbers of neutrophils and squamous epithelial cells, in consideration of the transplant recipient with neutropenia. Consultation with the patient's physician should be sought before sputum specimens are rejected. In addition to Gram stain and routine culture, specimens should be processed for acid-fast stain and culture, as well as direct fluorescent antibody (DFA) stain and culture for *Legionella* spp. Sputum cultures that yield *Aspergillus* spp. should be considered significant until proven otherwise (122); however, expecterated sputum is generally less helpful in the diagnosis of fungal and viral pathogens or infections caused by *Nocardia* spp.

BAL or bronchial biopsy provides a more reliable and accurate means of diagnosing pulmonary infection and is a relatively safe procedure in solid organ and BMT recipients (68). As a rule, BAL allows the sampling of inflammatory cells, secretions, and microorganisms from approximately 1 million alveoli (53). In renal transplant patients, BAL has a diagnostic accuracy of 66 to 93% (267). These specimens deserve exten-

sive cytologic and microbiologic evaluation. The design of special protocols (see below), which include a battery of tests to be routinely applied to BAL specimens, can ensure that these specimens are processed appropriately by the laboratory. Smears and cultures for aerobic bacteria, mycobacteria, fungi, viruses, *Nocardia* spp., and *Legionella* spp. should always be performed. BAL fluid may be examined for *P. carinii* by either the pathologist or the microbiologist. Commonly used histologic stains include Giemsa and Gomori methenamine silver, which stain trophozoites and cyst walls, respectively (19). Immunologic staining with monoclonal antibodies specific for *P. carinii* may allow a more accurate diagnosis than histochemical staining. Commercial products for IFA staining are now available and some have been evaluated (180).

The diagnosis of fungal infection in the solid organ transplant or BMT recipient involves one or more of three approaches: (i) isolation of the organism, (ii) serologic detection of antibody or antigen, and (iii) histopathologic evidence of invasion (273). Lysis centrifugation enhances the recovery of fungi from blood; however, *Aspergillus* spp. are exceptions, since they are rarely recovered from blood. Studies have shown that lysis centrifugation is superior to broth-based blood culture systems for the recovery of fungi as well as mycobacteria (24, 127). While lysis centrifugation may be too expensive and labor-intensive for the laboratory to use on all blood cultures, consideration should be given to reserving the method for use on samples from immunosuppressed patients. The isolation of fungi from otherwise sterile sites provides vital information to the clinician. In some cases, these cultures are positive in patients in whom fungemia was unexpected (102).

A plethora of fungal serologic tests have yielded variable success in the early diagnosis of fungal infections in transplant recipients (Table 4). Detection of host antibody to *Candida* spp. is of little value in the diagnosis of invasive disease (64). Tests to detect circulating candidal antigens have been studied extensively, but their value remains controversial (64, 289). The finding of circulating antibodies to *Aspergillus* spp. is useful in the detection of allergic bronchopulmonary disease and aspergilloma but not in the early detection of invasive disease (9). Although the detection of circulating antigen may correlate with invasive disease, after years of extensive investigation such tests are still considered experimental (9, 218). Conversely, the latex agglutination test for detection of circulating polysaccharide antigen of *Cryptococcus neoformans* is a reliable means of diagnosis and can also provide an indication of the

TABLE 4. Serologic tests for fungal infections<sup>a</sup>

Disease	CF	ID	TA	IFA	TP	LA (Ab)	LA (Ag)	EIA (Ab)	EIA (Ag)	RIA (Ab)	RIA (Ag)
Aspergillosis (invasive)	+ (CA)	+ (CA)						++	++	+	++
Blastomycosis	+ (CA)	+ (CA)						++ (CA)			
Candidiasis		+ (CA)				+	+ (CA)	+	++		++
Coccidioidomycosis	+++ (CA)	+++ (CA)			++	+++ (CA)		++ (CA)	++		
Cryptococcosis			+ (CA)	+			+++ (CA)		+++ (CA)		
Histoplasmosis	+++ (CA)	+++ (CA)					++ (CA)	++ (CA)			++
Paracoccidioidomycosis	+++	+++						++			
Sporotrichosis			+++			+++ (CA)		++			
Zygomycosis		+						+			

<sup>a</sup> Abbreviations: CF, complement fixation; ID, immunodiffusion; TA, tube agglutination; TP, tube precipitins; LA, latex agglutination; EIA, enzyme immunoassay; RIA, radioimmunoassay; Ab, antibody; Ag, antigen. Symbols: +++, can provide strong presumptive evidence of active disease; test has proven diagnostic and/or prognostic value; ++, can provide presumptive evidence of active disease; test has potential diagnostic and/or prognostic value; +, occasionally provides evidence of active disease; test has limited diagnostic and/or prognostic value. CA, commercially available.

patient's response to therapy (258, 277). Likewise, the detection of *Histoplasma capsulatum* antigen in serum and urine is also useful for the early diagnosis of disseminated histoplasmosis (295).

The diagnostic approaches toward the transplant recipient with a suspected viral infection include serologic testing, culture, and histologic examination of tissue. As discussed above, serologic techniques are helpful during the pretransplantation period for screening both recipients and donors for past exposure to a variety of viral agents. The usefulness of serodiagnosis in the acutely infected recipient, however, is limited by the lag time necessary for an immunologic response to occur. Moreover, the immunosuppressive state of the posttransplant patient may prevent the development of a detectable antibody response. With the advent of efficacious antiviral agents, such as acyclovir and ganciclovir for the treatment of HSV and CMV, respectively, an emphasis has now been placed on virologic diagnosis of these agents, rather than waiting for serologic conversion (225).

The length of time necessary for some viruses, particularly CMV, to exhibit cytopathic effect in cell culture makes the use of classic virology methods suboptimal when evaluating the transplant patient. Modalities that combine spin-amplified culture with direct antigen detection methods by IFA or ELISA should be applied during the virologic evaluation of transplant patients, especially on BAL, urine, and blood specimens. The shell vial technique for the detection of CMV produces an increase in infectivity of the viral inoculum and, when combined with an IFA stain for immediate-early antigen, can provide a diagnosis in 24 to 48 h (107). Two new techniques, the antigenemia assay and PCR, are useful for the early detection of CMV viremia. The antigenemia assay uses monoclonal antibodies directed against the pp65 matrix/tegument protein of CMV and is applied directly to buffy coat preparations. The number of positive granulocytes and monocytes seems to correlate with the degree of symptomatic disease, and studies have shown that the assay is positive for up to 1 week preceding

symptomatic disease (275). Detection of CMV viremia by PCR represents another approach to the detection and quantitation of CMV viremia (74, 90), and efforts to make PCR more "user-friendly" are continuing.

Advances in the rapid and accurate diagnosis of viral infections have allowed the incorporation of virology services into hospital microbiology laboratories that, despite little or no prior virology experience, can service the needs of expanding transplantation programs. Not surprisingly, the technological developments in the laboratory diagnosis of viral infections, such as shell vial assay and spin amplification, have been focused on the human herpesvirus group, especially CMV, HSV, and VZV, because these viruses are common opportunists in the transplant recipient. These techniques can be used for the detection of many viruses from a variety of specimen types. New techniques, such as the CMV antigenemia assay and genome detection by PCR, are still in the experimental stage, and their adaptation by laboratories will ultimately be determined by their clinical utility, commercial availability, and cost.

#### Use of Special Microbiologic Protocols

Laboratory diagnosis of infection in the transplant recipient can be facilitated by the use of established protocols for specific specimen types or specific clinical presentations. The use of established protocols ensures that critical specimens will be processed appropriately, and they are especially compatible with invasive procedures that obtain limited quantities of tissue, because these procedures may be risky to the patient. Protocols should provide testing for both common and uncommon pathogens and generally should combine histologic examination, special stains, and culture. An example of such a protocol for processing pulmonary specimens such as BAL fluid and lung biopsy specimens is shown in Table 5. Occasionally, there is interest in performing quantitative cultures of BAL fluids or tissue obtained by protected specimen brush. Recent studies have examined the utility of using specific colony

TABLE 5. Processing protocol for BAL and biopsy specimens from transplant recipients

Microscopy	Cultures	Other <sup>a</sup>
Gram stain	Routine aerobic bacteria	Mycoplasmas
Kinyoun stain	Fungi	<i>Chlamydia pneumoniae</i>
Calcofluor white stain	Mycobacteria	Quantitative culture
DFA for <i>Legionella</i> spp.	<i>Legionella</i> spp.	CMV PCR
Silver stain for <i>P. carinii</i>	Viruses (including shell vial culture for detection of CMV immediate-early antigen)	RSV IFA or ELISA

<sup>a</sup> Requires special request.

counts of aerobic bacteria as a means of distinguishing colonization from true infection. A cutoff of  $10^5$  CFU per ml of BAL or  $10^3$  CFU per brush specimen is considered significant (119). Complexities of dilution and attendant difficulties in interpretation, however, make these procedures experimental. Laboratories should consult closely with the ordering physician before such tests are undertaken.

### Monitoring of Asymptomatic Transplant Recipients

The use of microbiological surveillance protocols for monitoring the asymptomatic transplant patient should be developed with consideration of (i) the probability and severity of a particular infection in the patient population; (ii) the time after transplantation during which the risk of infection exists; (iii) the accuracy and costs of tests available for surveillance; (iv) the clinical importance of a positive test result in an asymptomatic patient and that in a patient tested at the first sign of disease; (v) the efficacy of prophylactic therapy as well as the risk of development of resistance; and (vi) the expected impact on the patient's clinical outcome (286). The use of routine surveillance cultures as a means of early detection of bacterial and fungal infections in transplant recipients during the early postoperative phase may be offset by the use of selective mucosal decontamination (225). Such cultures, however, may still be helpful for monitoring antibiotic resistance or patient compliance (286).

As the diagnosis of candidiasis prior to death is possible in less than half of immunocompromised patients (61), the utility of surveillance for earlier prediction or diagnosis of candidal infection has been an area of great interest. Sites and specimens commonly cultured as a means of surveillance include blood, sputum, stool, urine, throat, nasopharynx, rectum, and skin. Although surveillance methods are used in many organ transplant programs, their ability to predict future invasive disease remains debatable. It has been shown that BMT and leukemic patients, patients who develop disseminated candidiasis have a very high incidence of positive surveillance cultures for *Candida* spp. prior to the diagnosis of disseminated disease (123, 220, 279, 282, 299). Colonization without invasion, however, is also common in this population, and many patients with positive surveillance cultures never develop invasive disease. This finding is supported by studies in BMT patients and patients with hematologic malignancies which show a poor positive predictive value for the isolation of *Candida albicans* from surveillance cultures (203, 216, 233). The positive predictive value for the finding of *Candida tropicalis* may be higher (233). These studies did show a significant negative predictive value for surveillance cultures for *Candida* spp., and thus negative surveillance cultures may be of help to the clinician (203, 216, 233). Among solid organ recipients, a study in liver transplant patients likewise showed poor correlation between positive surveillance cultures and invasive infection (278).

The greatest utility of surveillance cultures may be as an epidemiologic tool to provide information regarding the microbiological milieu in a particular ward or hospital, which may aid with infection control measures and help guide the selection of empirical and prophylactic antifungal agents (30). The recurrent isolation of *Candida* species typically resistant to fluconazole, *Candida krusei* and *Torulopsis glabrata*, for example, may be of significance in a transplant unit that relies upon fluconazole as a prophylactic agent and may prompt the use of amphotericin B as prophylaxis or encourage earlier treatment with amphotericin B in the patient with suspected invasive disease. More sophisticated methods of DNA typing will probably be applicable to surveillance data in epidemiological stud-

ies, as colonizing and infecting strains may be more precisely characterized.

The poor sensitivity for the early recovery of *Aspergillus* spp. from routine culture specimens limits the use of surveillance methods for the early detection of infection. When an *Aspergillus* sp. is found in a respiratory specimen, its significance is often questioned, because it may represent contamination. The conclusion drawn from several studies is that a positive respiratory culture for *Aspergillus* in a host with predisposing factors is highly suggestive of invasive disease (27, 133, 177, 219, 309). It has also been noted that although false-positive sputum cultures are common, multiple positive cultures are more indicative of true infection than is a single positive culture (291). Therefore, a positive sputum culture in a neutropenic BMT patient or in a solid organ transplant recipient undergoing treatment for rejection should prompt a thorough evaluation and institution of empirical antifungal therapy.

The ability of surveillance methods to adequately predict the development of clinically significant disease due to the herpesviruses has been difficult in view of their characteristic of latency. The isolation of HSV from most specimens is of unclear significance. One study has shown that the isolation of HSV from urine preceded primary disease in a group of renal transplant recipients (72). The finding of HSV viremia may be of greater significance, but it is rare unless infection is already disseminated (178). Foreseeing active EBV disease is similarly difficult, although there is evidence that increased replication and mucosal shedding may precede overt disease (224, 225). Less is known regarding the diagnosis or surveillance of infection due to HHV-6. Changes in antibody titers do not appear to be predictive of HHV-6 lung disease (48), and antibody production is poor in BMT patients (305). There is therefore no established protocol for surveillance of these viruses.

Surveillance methods to help in the early diagnosis or in the targeting of particular groups of patients in imminent danger of active infection due to CMV have generated more interest due to the greater morbidity and mortality attributed to this virus than to other members of the group. Unfortunately, these efforts have been plagued by difficulties in interpretation of serologic data in immunocompromised patients, inconsistency in the definition of "infection" and "disease," and the unclear significance of isolation of a latent virus. Diagnosis still depends upon tissue biopsy and histologic evidence of viral infection and typical cellular changes.

The application of surveillance techniques for CMV has been studied most closely in the BMT population. Two studies have shown that patients with positive throat, blood, urine, or BAL cultures for CMV prior to the onset of clinical disease benefited from treatment with ganciclovir when compared to those receiving placebo (93, 236). Approximately 12% of patients in both studies, however, developed CMV disease despite negative surveillance cultures. Another study of surveillance of blood, urine, and oropharyngeal cultures in BMT patients revealed CMV viremia to be predictive of symptomatic CMV disease, although 32% of patients developed disease without viremia (159). Two similar studies in renal transplant recipients (90, 204) again suggested that CMV viremia is highly specific but poorly sensitive in the prediction of clinical disease. Although methods for the early detection of CMV, such as antigen detection and PCR, may provide earlier detection of the virus, a correlation with active disease is unclear. Prolonged PCR positivity has been noted in the absence of clinical disease (90). This method may be too sensitive in the detection of this common latent virus and thus not suited for use in surveillance.

The use of preemptive therapy in the approach to the CMV



problem appears to hold promise. The identification of a particular patient population at greatest risk of infection for the administration of preemptive therapy must be based upon a constellation of risk factors and clinical judgment of the physician, in addition to surveillance data from the laboratory.

PCR has also been applied to the identification of proliferating hepatitis viruses. The presence of HBV DNA, however, has not correlated well with hepatic dysfunction (185). Once again, the presence of HBV or HCV does not necessarily indicate causation or provide reliable information about future disease activity, and tissue biopsy remains necessary for the accurate assessment of the degree of viral activity and extent of hepatic damage in patients infected with HBV and HCV.

One of the keys to the survival and prosperity of transplant medicine is the ability of the microbiology laboratory to provide the clinician with vital information about infection. As laboratory methods evolve and become more accurate and timely in the identification of opportunists, the prevention and treatment of infection in the transplant recipient will become more successful. This can be expected to decrease the morbidity and mortality associated with organ transplantation and lead to more extensive applications of this life-saving treatment modality.

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