IMMUNOCOMPROMISED HOSTS   INVITED ARTICLE

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Opportunistic Infections in Patients with and Patients without Acquired Immunodeficiency Syndrome

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In the next decade, longer survival of patients with cancer and more-aggressive therapies applied to common conditions, such as asthma and rheumatoid arthritis, will result in a larger population with significant immune system defects. Many in this population will be at risk for opportunistic infections, which are familiar to doctors who have treated people infected with human immunodeficiency virus (HIV). However, the epidemiology, presentation, and outcome of these infections in patients with an immune system defect, other than that caused by HIV infection, may be different than those encountered in patients with acquired immunodeficiency syndrome. Reviewed are 4 common opportunistic infections: *Pneumocystis carinii* pneumonia, cryptococcosis, atypical mycobacterial infection, and cytomegalovirus infection. Emphasized are the important differences among these groups at risk.

Many physicians have treated opportunistic infections (OIs) in patients with AIDS and are familiar with clinical presentation in and management of this population. However, OIs continue to occur in persons who have cancer, or collagen vascular disease or have received organ transplants. In addition, relatively common diseases, such as asthma, inflammatory bowel disease, and rheumatoid arthritis, are being treated with increasingly cytotoxic medications, such as methotrexate and cyclosporine, or with anti-inflammatory monoclonal agents that may predispose the patient to OIs [1]. Furthermore, bone marrow transplantation is being applied to nonneoplastic conditions, such as sickle cell disease, thalassemia, and multiple sclerosis. Thus, in the years ahead, an expanding proportion of the US population will be treated with immunosuppressive therapy, placing many at risk for OIs.

This review will consider differences in the epidemiology, clinical presentation, and outcome for 4 OIs common in patients with AIDS: *Pneumocystis carinii* pneumonia (PCP); infection with *Cryptococcus neoformans;* infection with atypical mycobacteria, especially *Mycobacterium avium* complex (MAC); and in-

fection with cytomegalovirus (CMV). Each will be considered in the context of specific risk groups.

Prevention of OIs among persons without AIDS also will be briefly discussed. Information on prophylaxis can be obtained in the form of Public Health Service guidelines for persons with HIV/AIDS [2] and persons who have undergone hematopoietic stem cell transplantation (HSCT) [3]. No guidelines for other risk groups are available.

PCP

Table 1 shows the incidence and outcomes of PCP in patients with and patients without HIV infection.

Epidemiology

AIDS. Prior to routine use of prophylaxis, most HIV-infected persons with CD4 counts of <200 cells/mm^3 developed PCP [4]. Although the rate has decreased significantly with the introduction of HAART, PCP remains the most common AIDS-related OI, usually occurring among those not receiving primary care [22].

Cancer. Hughes et al. [6], in their seminal studies of PCP in children with acute lymphoblastic leukemia (ALL), found an incidence ranging from 22% to 45%, depending on the chemotherapy used and the stage of leukemia. With the introduction of prophylaxis, the rate decreased to 0% [23]. Without

Table 1. Incidence, clinical presentation, outcome, and prevention of *Pneumocystis carinii* pneumonia (PCP) among patients who did not receive prophylaxis and did or did not have HIV infection.

Variable	Patient group, by disease or condition				
	AIDS	Cancer[a]	Transplantation[a]	CVD	Other
Incidence	>50% [4]	Varies by type of cancer [5]; 22%–45% for ALL [6] and NHL [5], >25% for SCID [5], 25% for rhabdomyosarcoma [5], 1.3% for solid tumor while receiving CS [7]	5%–10% for all [5, 8–10]; >25% for lung transplant recipients [11, 12]	<2% for all types [13]; >6% for Wegener's granulomatosis [13, 14]	No data available; reports in the early 1990s described PCP without underlying immunodeficiency [15, 16]
Clinical presentation [17, 18]					
Prodrome duration, days	28	<5	<5	<5	NA
Po$_2$, mm	69	50	50	NA	NA
Parasite load	Many	Few	Few	Few	Few
Outcome: survival rate	>80%	50% [5]	90% of kidney transplant recipients [19]	68% [13]	NA
Preventive measures[b]	Patients with CD4 counts of <200 cells/mm³ [2] or a history of thrush [2]	>20 mg of a prednisone equivalent for >1 month [5]	Allo BMT recipients: during months 2–6, longer if there is chronic GVHD [3]; auto BMT recipients: consider for patients with intense conditioning or recent use of fludarabine, Campath antibodies, or a similar compound [3]; SOT recipients: during the period of maximal immunosuppression [20, 21]	NR	NR

NOTE. ALL, acute lymphocytic leukemia; allo, allogeneic; auto; autologous; CS, glucocorticosteroids; CVD, collagen vascular disease; GVHD; graft-versus-host disease; NA, no data available; NHL, non-Hodgkin's lymphoma; NR, no recommendation; Po$_2$, partial pressure of oxygen; SCID, severe combined immune deficiency; SOT, solid-organ transplant.

[a] Rate related to intensity of chemotherapy or immunosuppressive therapy used (see the section on PCP in the text).

[b] Preventive measures recommended for the at-risk patients who meet the criterion or criteria specified.

prophylaxis, rates may approach 25% among patients with non-Hodgkin's lymphoma, severe combined immunodeficiency syndrome, or rhabdomyosarcoma [5]. The incidence among persons with a primary or metastatic CNS tumor is 1.3% [7]. Generally, corticosteroid use is implicated; recent reports, however, suggest that increasingly potent cytoreductive therapy, without corticosteroids, may be sufficient [24, 25].

Transplantation. Without prophylaxis, PCP develops in 5%–15% of patients who undergo solid-organ transplantation or allogeneic HSCT [5, 8-10]. Among heart-lung transplant and lung transplant recipients, the rate is higher, approaching 25% in most series [11, 12]. PCP is uncommon among autologous HSCT recipients [2]. Organ rejection may increase the risk [26]. More-potent immunosuppression has resulted in higher rates among heart and kidney transplant recipients [27, 28]. Nosocomial transmission has occurred in kidney transplant recipients [29].

Other. PCP occurs in 1%–2% of all patients with rheumatologic disorders—most often, but not always, among those receiving immunosuppressive therapy [13]. Patients with Wegener's granulomatosis are at higher risk, with rates up to 6% [13, 14]. Isolated cases have been reported for persons receiving intense immunosuppression for asthma, glomerulonephritis, ulcerative colitis, and other conditions [5].

No known immunodeficiency. In the 1990s, series from New York [15] and Spain [16] described PCP in patients who had no clear predisposition. No similar cases have subsequently been reported.

Clinical Presentation

Kovacs and colleagues [17] published a landmark study contrasting the clinical characteristics of PCP in 49 HIV-infected persons with those in 39 HIV-negative patients who had other underlying conditions. At presentation, patients with AIDS had a longer median duration of symptoms (28 vs. 5 days) and higher median room air arterial oxygen tension (69 vs. 52 mm Hg). Subsequent studies have confirmed the differences.

Outcome

The survival rate among patients with PCP and AIDS has improved steadily; it now approaches 90% in many treatment centers. In sharp contrast, survival among patients with PCP who do not have HIV infection has improved little: only 40%–70% survive. In the 1970s, Hughes et al. [30] found a 68% survival rate among children with acute lymphoblastic leukemia, and Walzer et al. [31] reported a 42% survival rate among all reported cases in the United States. Throughout 3 decades of reports from Memorial Sloan-Kettering Cancer Center (MSKCC; New York), the survival rate has been ~50%, although it has improved recently [7, 25].

Mortality rates vary according to the population at risk, with patients with cancer faring the worst [7, 17]. A report from a Dutch center found a 65% survival rate overall among 78 HIV-negative patients, with the best rate (92%) among 13 kidney transplant recipients [19]. A comparable survival rate was described in a study from the Mayo Clinic [32] and for rheumatology patients [13].

Limper and colleagues [18] investigated a possible pathophysiologic basis for the differences in presentation and outcome. They examined the numbers of *P. carinii* parasites and the lung inflammatory cell populations in bronchoalveolar lavage specimens obtained from patients with and patients without AIDS. The investigators found that patients with AIDS had significantly higher numbers of *P. carinii* and substantially fewer neutrophils in the lavage fluid samples than did other immunocompromised patients with PCP. They hypothesized that the number of neutrophils negatively influenced overall survival, concluding that lung inflammation contributed to respiratory impairment in patients with PCP. According to this hypothesis, HIV-negative patients with PCP have higher rates of complication and death, paradoxically, because they have a superior capacity for inflammation. Alternatively, other more complex and less conspicuous factors may account for the difference.

Prevention

Trimethoprim-sulfamethoxazole is the preferred prophylactic agent in any patient population [2, 3, 33]. Desensitization is effective in ≥65% of HIV-infected persons who report an allergy [34] and may be effective in persons at risk with other conditions, [35] except those with a history of a blistering rash from sulfa drug exposure. The optimal duration of prophylaxis remains unsettled [3, 20, 21]. Treatment with alternative medications, such as dapsone, aerosolized pentamidine, sulfadoxine-pyrimethamine, and atovaquone, appears effective in some populations [36–39] but inferior in others [40, 41].

Determining which HIV-negative patients are at risk for PCP remains difficult [42]. A decreased CD4 cell count may suggest risk [43], as does receipt of high doses of corticosteroids for an extended period. However, many patients receive brief courses of corticosteroids for such conditions as asthma. Their risk of an adverse reaction to trimethoprim-sulfamethoxazole certainly outweighs any potential benefit. At MSKCC, patients who have an underlying immunocompromising condition, such as cancer, who receive the equivalent of ≥20 mg of prednisone for ≥1 month are given trimethoprim-sulfamethoxazole at the institution of the corticosteroid course and for 1 month after its discontinuation [5, 42].

C. NEOFORMANS INFECTION

Table 2 lists incidence and outcome of *C. neoformans* infection in patients with and patients without HIV infection.

Table 2. Incidence, clinical presentation, outcome, and prevention of invasive cryptococcosis among patients who did not receive prophylaxis and did or did not have HIV infection.

Variable	Patient group, by disease or condition			
	AIDS	Cancer	Transplantation	Other
Incidence	1700–6600 cases per 100,000 patients [44]; 5% [45]	0.5 cases per 100,000 admissions to MSKCC [46]	0.3%–2% in liver transplant recipients [47, 48], but 6% in those treated with tacrolimus [49]	0.2–0.9 cases per 100,000 for US population [44]; rare but seen in patients with diabetes or receiving corticosteroids [44]
Clinical presentation	Meningitis predominates; fungemia less common	Meningitis predominates; fungemia less common	Cutaneous and/or osteoarticular disease; meningitis [49, 50]	NA
Outcome: survival rate	78% [51]; 70% [52]	43% [51]; 60%–70% [53]; increased hazard ratio (7.49) [54]	NA	NA
Preventive measures	Although oral azole therapy may prevent disease, it has no impact on mortality, and, therefore, is not recommended [2]	NR	NR	NR

NOTE. MSKCC, Memorial Sloan-Kettering Cancer Center (New York); NA, no data available; NR, no recommendation.

Epidemiology

AIDS. Invasive cryptococcosis occurs annually in 0.2–0.9 per 100,000 persons not infected with HIV and in 1700–6600 per 100,000 persons with AIDS [44]. Before the introduction of HAART, as many as 5% of all HIV-infected persons developed cryptococcosis [45]. Since then, the incidence has decrease by approximately one-half [22].

Cancer. Several series have demonstrated that patients with cancer, especially those with lymphoma and chronic leukemia, are at increased risk for invasive cryptococcosis, particularly meningitis [44]. During 21 years at MSKCC (1979–1999), 23 cases (excluding isolated pulmonary disease) have occurred in patients with neoplastic disease, for a rate of ~8.5 cases per 100,000 hospital discharges during the past decade [46, 51]. Underlying diseases have included non-Hodgkin's lymphoma (in 9 patients), Hodgkin's lymphoma (in 7 patients), chronic lymphocytic leukemia (in 3 patients), and other diagnoses (in 4 patients).

Transplantation. Invasive cryptococcosis occurs in 0.3%–2% of liver transplant recipients [47, 48], although 1 study reported disease in 6 (6%) of 102 consecutive liver transplant recipients who received tacrolimus [49]. Disease is less-commonly described among kidney and heart transplant recipients in the United States; a report from India described cryptococcosis in 9 (2.9%) of 310 kidney transplant recipients [55].

Other. Rare cases of disseminated cryptococcal disease are seen among persons receiving corticosteroid therapy for any indication [54, 56] and in those with diabetes mellitus [44]. Rates are unknown.

No known immunodeficiency. All series report cryptococcosis among patients who lack a clear predisposition [54, 57, 58]. Older series suggested that such "normal" hosts accounted for up to 20% of meningitis cases and 80% of cases of CNS cryptococcal abscess [59]. In a recent study of cryptococcosis in 135 persons without HIV infection, 30% had no discernible underlying condition [44].

Clinical Presentation

The presentation of cryptococcal meningitis is similar in groups at risk; fever, change in mental status, and headache occur in >50% of patients at risk. Meningismus is uncommon. In some studies, patients with HIV infection are more likely to have fungus evident on India ink examination and a higher cryptococcal latex agglutination titer [58]. In addition, the intensity of inflammation in HIV-infected patients, as measured by CSF WBC counts, may be lower than it is in persons without HIV infection. Among both liver and kidney transplant recipients, cryptococcus infection may cause cutaneous and/or osteoarticular disease; meningitis is less common [49, 50, 55].

Cryptococcus subspecies may influence both clinical presentation and outcome in persons without HIV infection; *C. neoformans* var. *gatti* perhaps has a more-severe presentation and a worse outcome [57, 60]. Such insights into virulence may explain differences in presentation across a wide range of pathogens, but data remain limited.

Outcome

A series from MSKCC reported a significant difference in outcomes for persons with cryptococcal meningitis according to underlying HIV status [51]. Persons with cryptococcal meningitis and cancer fared significantly worse than did those with HIV infection (improvement or cure in 43% vs. 78%), a finding similar to that for persons with PCP.

French investigators found the strongest predictor of fatal infection among 83 HIV-negative patients with cryptococcosis was underlying cancer ($P = .007$; hazard ratio, 7.49) [54]. The

survival rate was higher among those who had undergone organ transplantation, who had a variety of other conditions, or who had no discernible abnormality.

Prevention

Routine prophylaxis is not recommended against cryptococcosis for any risk group.

ATYPICAL MYCOBACTERIAL INFECTIONS

Table 3 shows incidence and outcomes of atypical mycobacterial infections in patients with and patients without HIV infection.

Epidemiology

Rapidly growing mycobacteria are well known to cause central venous catheter–related bacteremia [63, 73]. These infections are related to anatomic disruption and not to an underlying immune system defect and, therefore, will not be considered further. Non–catheter-related disease due to the rapidly growing mycobacteria is quite rare; such infections have occurred in a wide variety of underlying conditions [72].

AIDS. Before HAART was introduced, atypical mycobacterial infection, particularly MAC infection, was common among patients with advanced AIDS. For example, disseminated MAC occurred in ∼25% of patients with <50 CD4 cells/mm^3 [2]. With use of effective prophylaxis and HAART, this rate has decreased significantly [22]. Numerous other atypical mycobacteria have been reported to cause both disseminated and pulmonary disease in patients with HIV infection [74].

Cancer. Disseminated MAC is seldom encountered in patients with cancer [75], with the exception of those with hairy cell leukemia [61] or, perhaps, chronic myelogenous leukemia (CML) [62]. In separate series, 9 (5%) of 186 patients with hairy cell leukemia [61] and 3 (4%) of 76 patients with CML [62] developed disseminated atypical mycobacterial infection, usually MAC infection.

Rapidly growing mycobacteria (*Mycobacterium fortuitum* and *Mycobacterium chelonae)* were recovered from respiratory specimens obtained from 37 patients with various cancers at The University of Texas M. D. Anderson Cancer Center (Houston, TX); most culture results were thought to indicate colonization [76]. In the last 8 years at MSKCC, only 1 patient with cancer has developed MAC bacteremia, a 5-year-old child receiving intensive chemotherapy (which included cladribine) for histiocytosis.

HSCT. Of 6259 patients who underwent HSCT in Seattle the past 20 years, 5 patients (0.07%) developed probable or definite mycobacterial disease, exclusive of catheter-related infection [63]. Infecting species included MAC (in 3 patients) and *Mycobacterium gordonae* (in 2 patients). Among 2241 HSCT recipients at the University of Minnesota, mycobacterial infections were diagnosed in only 11 (0.49%), including 9 (0.6%) of 1486 allograft recipients and 2 (0.26%) of 755 autograft recipients [64]. Infecting mycobacteria included *Mycobacterium tuberculosis* (in 2 patients), MAC (in 2 patients), and rapidly growing mycobacteria (in 7 patients; 6 of these infections were related to central venous catheters).

In the 1990s at MSKCC, 812 allogeneic HSCTs were performed, including many with T-cell depleted allogeneic grafts. The only atypical mycobacteria that caused bacteremia was *Mycobacterium haemophilum;* bacteremia due to this organism was diagnosed in 13 (1.6%) of these cases [69].

Kidney transplantation. In older series, mycobacterial infections complicated 0.3%–0.5% of kidney transplantations [65]; however, many of these infections were tuberculosis. In 1 report, approximately one-half of the infections occurred in the first 6 months after transplantation, in contrast to infections in patients who receive other solid-organ transplants, which typically occur much later [65]. Several reviews of the topic have appeared [68, 77].

Heart transplantation. Among patients who underwent heart transplantation at Stanford University (Palo Alto, CA) during the years 1968–1988, 14 (2.8%) of 502 patients developed mycobacterial infection; the majority of these cases occurred before the introduction of cyclosporine [66]. The time from transplantation to diagnosis was ∼3.5 years, and the patients with mycobacterial infection had higher rates of transplant rejection. Eight patients presented with disseminated infection, and 4 had findings localized to the lungs. The survival rate was comparable to that for other transplant recipients. Infecting species included *Mycobacterium kansasii,* in the early years of the program, and MAC, in the second decade.

Lung transplantation. In a series from Australia, 21 (8%) of 261 lung transplant recipients developed atypical mycobacterial disease, including MAC infection (13 pulmonary cases) and disseminated *M. haemophilum* infection (5 cases) [67]. Pulmonary infections typically involved the transplanted lung. Mean time from transplant to diagnosis was almost 2 years. Patients with mycobacterial infection showed a trend for graft rejection.

Liver transplantation. Atypical mycobacterial infection is seldom reported in liver transplant recipients [68].

Other conditions/no known immunodeficiency. Slowly progressive pulmonary infection with MAC has been described in middle-aged men with various comorbidities, particularly underlying lung disease [70]. Corticosteroid use rarely has been associated with disseminated MAC infection [75].

In 1989, a syndrome of progressive pulmonary MAC infection in persons without evident predisposing conditions was described [71]. Patients tended to be thin, elderly women, many of whom had axial skeletal abnormalities, such as scoliosis and pectus excavatum, as well as mitral valve prolapse [78].

Table 3. Incidence, clinical presentation, outcome, and prevention of atypical mycobacterial infections among patients who did not receive prophylaxis and did or did not have HIV infection.

Variable	Patient group, by disease or condition			
	AIDS	Cancer	Transplantation	Other
Incidence				
MAC infection	20%–25% if CD4 count is <50 cells/mm³ [2]	Very rare, except: 5% for hairy cell leukemia [61] and 3.9% for CML [62]	Allo BMT recipients, 0.07% [63]; allo and auto BMT recipients, 0.49% [64]; kidney transplant recipients, 0.3–0.5% [65] (includes TB); heart transplant recipients, 2.8% [66] (higher with cyclosporine); lung transplant recipients, 8.0% [67]; liver transplant recipients, very rare [68]	NA
Mycobacterium haemophilum infection	Rare [69]	Rare	Allo BMT, 1.6% [69]	NA
Clinical presentation				
MAC infection	Constitutional	Constitutional	Pulmonary [63]	Progressive pulmonary infection [70, 71]
M. haemophilum infection	Skin and joint symptoms [69]	NA	Skin lesions [69]; tenosynovitis, arthritis [68]; tenosynovitis, arthritis [68]	
Mycobacterium kansasii infection	Pulmonary, disseminated	NA	NA	Pulmonary in normal hosts
Infection due to rapidly growing pathogens	Catheter-associated	Catheter-associated [72]; disseminated [72]; skin lesions [72]	Catheter-associated; tenosynovitis, arthritis [68]	Wound-associated
Outcome	Most respond to effective therapy	Respond to effective therapy	No increased mortality, except for allo BMT recipients with *M. haemophilum* infection involving lungs [69]	Progressive disease despite therapy [70, 71]
Preventive measures[a]	CD4 count, <50 cells/mm³ [2]	NR	NR [3]	NR

NOTE. allo, allogeneic; auto, autologous; BMT, bone marrow transplantation; CML, chronic myelogenous leukemia; MAC, *Mycobacterium avium* complex; NA, no data available; NR, no recommendation.

[a] Preventive measures recommended for the at-risk patients who meet the criterion or criteria specified.

Clinical Presentation

The presentation of disseminated mycobacterial disease is similar in any patient group and is characterized by constitutional symptoms, such as fever, night sweats, weight loss, and fatigue. Clinically evident MAC infection of specific organs, such as lung, soft tissue, or the urinary tract, is unusual. With the introduction of HAART, symptomatic MAC adenitis has emerged as an "immune reconstitution syndrome" [79].

Among 78 cases of atypical mycobacteriosis in kidney and heart transplant recipients [68], cutaneous involvement, tenosynovitis, and arthritis were the most common presentations, accounting for 67% of cases. In contrast, classic constitutional signs, such as fever and weight loss, were unusual. Pulmonary involvement was encountered in only 28% of cases. *M. kansasii* and *M. haemophilum* accounted for the majority of infections.

Among HSCT recipients, *M. haemophilum* infection predominates. This infection may present with ulcerating, painful skin lesions, joint involvement, or, in more-severe cases, with pneumonitis and/or bacteremia [69]. The presentation of *M. haemophilum* infection in persons with HIV infection is identical. Involvement of the transplanted lung with progressive MAC pneumonitis is the most common presentation among lung transplant recipients [67].

Progressive pulmonary MAC infection among middle aged men with preexisting lung disease and among thin elderly women is characterized by productive cough, gradual weight loss, and an indolent but ineluctable course [70, 71].

Outcome

The introduction of macrolide antibiotics (clarithromycin and azithromycin) has provided agents potent against many atypical mycobacteria, resulting in effective therapy for most diseases. An exception is *M. haemophilum* infection involving the lung, which appears to be always fatal [69]. Potential drug-drug interactions, especially with rifamycins, complicate management of these infections in patients who have cancer or who have undergone transplantation.

Prevention

Routine prophylaxis against atypical mycobacteriosis for any risk group, other than patients with AIDS [2], is not recommended.

CMV INFECTION

Table 4 lists the incidence and outcomes of CMV infection in patients with and patients without HIV infection.

Epidemiology

AIDS.   In the early 1990s, the rate of CMV retinitis was 7.5 case per 100 person-years among people with AIDS; the rate for other symptomatic CMV disease was 4.5 cases per 100 person-years [22]. Introduction of HAART has resulted in a drastic decrease in the number of cases and has allowed many patients with existing disease to discontinue their anti-CMV therapy [22].

Cancer.   CMV disease is extremely rare in patients with cancer. A review from M. D. Anderson Cancer Center identified only 20 cases of CMV pneumonia among 9029 autopsies (a rate of 2.2 per 1000 autopsies) performed during 1964–1990 on adults without HIV or transplanted organs [80]. Cases were more common among patients with multiple myeloma (rate, 18.4 cases per 1000 autopsies) and brain tumor (rate, 10.1 cases per 1000 autopsies). All had received chemotherapy, and 75% had received corticosteroids. Most cases occurred in patients with disseminated neoplasm. An increased risk for patients with leukemia has recently been suggested [85].

At MSKCC, data for all patients treated between 1996 and 1998 who had a blood sample positive for CMV by culture, early antigen test, or shell vial culture were reviewed [89]. Results for >4500 tests were submitted, including many from 448 recipients of autologous transplants. After patients who had HIV infection or had received an allogeneic transplant were excluded, only 3 patients had high-grade antigenemia (defined as >15 cells/slide), each of whom was receiving high-dose corticosteroid therapy. Underlying conditions included acute lymphoblastic leukemia, chronic myelogenous leukemia, and Evans's syndrome.

Transplantation.   CMV disease is a serious complication in patients who undergo solid-organ transplantation or allogeneic HSCT. Without prophylaxis, 8%–39% of solid-organ transplant recipients (rates for kidney and heart-lung transplant recipients, respectively) and 20%–35% of allogeneic HSCT recipients develop disease that may result in graft rejection [81].

Other conditions/no known immunodeficiency.   Severe CMV infections have been reported rarely in seemingly immunocompetent persons [82, 83]. One review identified 34 such cases in the world literature [82]. Acute CMV infection may be more severe in some patients with lupus [84].

Clinical Presentation

CMV causes an infectious mononucleosis–like syndrome in normal hosts [82]. CMV retinitis is a familiar complication of advanced HIV infection, but is extremely unusual in other compromised hosts [82, 83]. Rare cases have been reported during intensive chemotherapy or immunosuppression [82, 83].

Similarly, CMV retinitis following either HSCT or solid-organ transplantation is uncommon. A report from Seattle found 10 cases in 5721 HSCT recipients [88]. Among persons who were alive at day 100 after transplantation and had chronic graft-versus-host disease, the rate was 1.4%. Fewer than 5 cases have occurred among the recipients of 812 allogeneic transplants performed during the past decade at MSKCC.

Among 860 patients who received heart, lung, or liver transplants in Australia, ~1% developed retinitis [90]. A large series from New York City found CMV retinitis in 4 of 684 liver transplant recipients [91]. Symptoms began, on average, 4 months after transplantation. Active surveillance may reveal

Table 4.   Incidence, clinical presentation, outcome and prevention of cytomegalovirus (CMV) infection among patients who did not receive prophylaxis and did or did not have HIV infection.

| Variable | Patient group, by disease or condition | | | |
	AIDS (pre-HAART)	Cancer	Transplantation	Other
Incidence	12 cases per 100 patients overall [22]; 7.5 cases per 100 patients for retinitis [22]	Rare; 2.2 cases per 1000 autopsies [80]; 18.4 cases per 1000 autopsies of patients with multiple myeloma [80]	Kidney transplant recipients, 8% [81]; heart-lung transplant recipients, 39% [81]; allo BMT recipients, 20%–35% (disease) [81]	40%–100% seroprevalence [82]; many subclinical cases; rare severe cases in normal hosts [82] and those with comorbidities [83]; rare in patients with lupus [84]
Clinical presentation	Retinitis, colitis, pneumotitis (rare)	Pneumonitis (rare) [80, 85]	Fever, pneumonitis [81], graft failure [81], GI involvement [86, 87], retinitis (rare) [88]	25% of "mono" cases [82]; severe invasive disease of multiple organs [82, 83]
Outcome	Relapse is common	NA	Pneumonitis in allo BMT recipients is fatal in 50% of cases [81]; graft rejection [81]	Poor outcome for severe disease [82, 83]
Preventive measures[a]	CD4 count <50 cells/mm^3 and CMV seropositive [2]	NR	Preemptive or prophylactic, per institutional protocol [3]	NR [82]

NOTE.   Allo, allogeneic; BMT, bone marrow transplantation; GI, gastrointestinal; HAART, highly active antiretroviral therapy; allo, allogeneic; "mono," syndrome consistent with infectious mononucleosis; NA, no data available; NR, no recommendation.

[a] Preventive measures recommended for the at-risk patients who meet the criterion or criteria specified.

more cases: among heart transplant recipients who were examined prospectively, 14.6% had evidence of retinitis that was ongoing or had resolved [92].

CMV pneumonitis resembles any diffuse pneumonitis [80]. CMV infection with gastrointestinal involvement is more frequently described (in ∼5% of all transplant recipients) and may involve any part of the gastrointestinal tract [86, 87].

The introduction of molecular-based diagnostic tests, such as the pp65 antigen test and PCR, has allowed clinicians to intervene early in the course of infection, resulting in better outcome [93]. However, the aggressive approach has spawned a new syndrome, "late CMV disease," which suggests that, for some patients, advent of symptoms is delayed by such therapy, not averted [94, 95].

Outcome

Complications from CMV infection usually relate more to the influence of CMV infection on graft survival than to end-organ CMV disease, except among HSCT recipients with CMV pneumonitis, who continue to have a high mortality rate (50%) [81]. Relapse occurs in up to one-fourth of all solid-organ transplant recipients who receive routine 2-week induction therapy.

Prevention

Routine prophylaxis against CMV infection is not recommended for patients with HIV infection, although the availability of active orally administered agents may cause this recommendation to be reconsidered [2]. The ability to detect low levels of CMV by PCR or antigen-capture testing prior to the development of invasive disease has profoundly changed the preventative strategies available for solid-organ transplant and HSCT recipients [93].

CONCLUSION

OIs in patients with cancer, patients who have received organ transplants, and patients with other immune deficiencies may differ substantially from the same diseases encountered in patients with HIV infection. In addition, the host's ability to mount an inflammatory response may, paradoxically, result in a worse outcome, a reminder of the complicated and sometimes double-edged nature of inflammation. Despite advances in the prevention and treatment of OIs in patients with AIDS, management of OIs in other hosts looms as a significant challenge for the infectious diseases specialist in the years ahead.

References

1. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor-necrosis factor α–neutralizing agent. N Engl J Med 2001; 345:1098–104.
2. Centers for Disease Control and Surveillance. 1999 USPHS/IDSA guidelines for prevention of opportunistic infections in persons infected with human immunodeficiency virus. MMWR Morb Mortal Wkly Rev 1999; 48(RR-10):1–66.
3. Centers for Disease Control and Surveillance. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: recommendations of the CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. MMWR Morb Mortal Wkly Rev 2000; 49(RR-10):1–125.
4. Centers for Disease Control and Prevention. Recommendations for prophylaxis against Pneumocystis carinii pneumonia for adults and adolescents infected with human immunodeficiency virus. MMWR Morb Mortal Wkly Rev 1992; 41 (RR-4):1–11
5. Sepkowitz KA, Brown AE, Armstrong D. Pneumocystis carinii pneumonia without acquired immunodeficiency syndrome: more patients, same risk. Arch Intern Med 1995; 155:1125–8.
6. Hughes WT, Feldman S, Aur RJA, et al. Intensity of immunosuppressive therapy and the incidence of Pneumocystis carinii pneumonitis. Cancer 1975; 36:2004–9.
7. Sepkowitz KA, Brown AE, Telzak EE, Gottlieb S, Armstrong D. Pneumocystis carinii pneumonia among patients without AIDS at a cancer hospital. JAMA 1992; 267:832–7.
8. Hardy AM, Wajszczuk CP, Suffredini AF, et al. Pneumocystis carinii pneumonia in renal transplant patients treated with cyclosporine and steroids. J Infect Dis 1984; 149:143–7.
9. Hofflin JM, Potasman I, Baldwin JC, Oyer PE, Stinson EB, Remington JS. Infectious complications in heart transplant recipients receiving cyclosporine and corticosteroids. Ann Intern Med 1987; 106:209–16.
10. Meyers JD, Flournoy N, Thomas ED. Nonbacterial pneumonia after allogeneic marrow transplantation: a review of ten year's experience. Rev Infect Dis 1982; 4:1119–32.
11. Dummer JS, Montero CG, Griffith BP, Hardesty RL, Paradis IL, Ho M. Infections in heart-lung transplants. Transplantation 1986; 41:725–9.
12. Gryzan S, Paradis IL, Zeevi A, et al. Unexpectedly high incidence of Pneumocystis carinii infection after lung-heart transplantation: implications for lung defense and allograft survival. Am Rev Respir Dis 1988; 137 :1268–74.
13. Godeau B, Coutant-Perronne V, Huong DLT, et al. Pneumocystis carinii pneumonia in the course of connective tissue disease: report of 34 cases. J Rheumatol 1994; 21:246–51.
14. Ognibene FP, Shelhamer JH, Hoffman GS, et al. Pneumocystis carinii pneumonia: a major complication of immunosuppressive therapy in patients with Wegener's Granulomatosis. Am J Respir Crit Care Med 1995; 151:795–9.
15. Jacobs JL, Libby DM, Winters RA, et al. A cluster of Pneumocystis carinii pneumonia in adults without predisposing illnesses. N Engl J Med 1991; 324:246–50.
16. Cano S, Capote F, Pereira A, Calderon E, Castillo J. Pneumocystis carinii pneumonia in patients without predisposing illnesses. Chest 1993; 104:376–81.
17. Kovacs JA, Hiemenz JW, Macher AM, et al. Pneumocystis carinii pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. Ann Intern Med 1984; 100:663–71.
18. Limper AH, Offord KP, Smith TF, Martin WJ II. Pneumocystis carinii pneumonia: differences in lung parasite number and inflammation in patients with and without AIDS. Am Rev Respir Dis 1989; 140:1204–9.
19. Arend SM, Kroon FP, van't Wout JW. Pneumocystis carinii pneumonia in patients without AIDS, 1980 through 1993: an analysis of 78 cases. Arch Intern Med 1995; 155:2436–41.
20. Arend SM, van't Wout JW. Prophylaxis for Pneumocystis carinii pneumonia in solid-organ transplant recipients—as long as the pros outweigh the cons. Clin Infect Dis 1999; 28:247–9.
21. Gordon SM, LaRosa, SP, Kalmadi S, et al. Should prophylaxis for Pneumocystis carinii pneumonia in solid-organ transplant recipients ever be discontinued? Clin Infect Dis 1999; 28:240–6.
22. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human

immunodeficiency virus–associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. Clin Infect Dis 2000; 30(Suppl):S5–14.

23. Hughes WT. Five-year absence of *Pneumocystis carinii* pneumonitis in a pediatric oncology center. J Infect Dis 1984; 150:305–6.

24. Kulke MH, Vance EA. *Pneumocystis carinii* pneumonia in patients receiving chemotherapy for breast cancer. Clin Infect Dis 1997; 25:215–8.

25. Sepkowitz KA, Cicogna C, Armstrong D. *Pneumocystis carinii* pneumonia (PCP) at a cancer hospital, 1990–98: changing trends and improved survival [abstract]. In: Proceedings and abstracts of the 2000 American Lung Association/ American Thoracic Society International Conference (Toronto). 2000.

26. Arend SM, Westendorp RGJ, Kroon FP, et al. Rejection treatment and cytomegalovirus infection as risk factors for *Pneumocystis carinii* pneumonia in renal transplant recipients. Clin Infect Dis 1996; 22:920–5.

27. Olsen SL, Renlund DG, O'Connell JB, et al. Prevention of *Pneumocystis carinii* pneumonia in cardiac transplant recipients by trimethoprim sulfamethoxazole. Transplantation 1993; 56:359–62.

28. Lufft V, Kliem V, Behrend M, Pichlmayr R, Koch KM, Brunkhorst R. Incidence of *Pneumocystis carinii* pneumonia after renal transplantation: impact of immunosuppression. Transplantation 1996; 62:421–3.

29. Chave J-P, David S, Wauters J-P, Van Melle G, Francioli P. Transmission of *Pneumocystis carinii* from AIDS patients to other immunosuppressed patients: a cluster of *Pneumocystis carinii* pneumonia in renal transplant recipients. AIDS 1991; 5:927–32.

30. Hughes WT, Price RA, Kim HK, Coburn TP, Grigsby D, Feldman S. *Pneumocystis carinii* pneumonitis in children with malignancies. J Pediatr 1973; 82:404–15.

31. Walzer PD, Perl DP, Krogstad DJ, Rawson PG, Schultz MG. *Pneumocystis carinii* pneumonia in the United States: epidemiologic, diagnostic, and clinical features. Ann Intern Med 1974; 80:83–93.

32. Yale SH, Limper AH. *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illnesses and prior corticosteroid therapy. Mayo Clin Proc 1996; 71:5–13.

33. Munoz P, Munoz RM, Palomo J, Rodriguez-Creixems M, Munoz R, Bouza E. *Pneumocystis carinii* infection in heart transplant recipients: efficacy of a weekend prophylaxis schedule. Medicine (Baltimore) 1997; 76:415–22.

34. Para MF, Finkelstein D, Becker S, Dohn M, Walawander A, Black JR. Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for *Pneumocystis carinii* pneumonia. AIDS Clinical Trials Group 268. J Acquir Immune Defic Syndr 2000; 24: 337–43.

35. Walter E, Chauncey T, Boeckh M, Hackman R, Kennedy M, Bowden R. *Pneumocystis carinii* prophylaxis after marrow transplantation: efficacy of trimethoprim sulfamethoxazole (TS) and role of TS desensitization and intravenous pentamidine [abstract 32]. 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy (New Orleans). 1993.

36. Maltezou HC, Petropoulos D, Choroszy M, et al. Dapsone for *Pneumocystis carinii* prophylaxis in children undergoing bone marrow transplantation. Bone Marrow Transplant 1997; 20:879–81.

37. Nathan SD, Ross DJ, Zakowski P, Kass RM, Koerner SK. Utility of inhaled pentamidine prophylaxis in lung transplant recipients. Chest 1994; 105:417–20.

38. Colby C, McAfee S, Sackstein R, Finkelstein D, Fishman J, Spitzer T. A prospective randomized trial comparing the toxicity and safety of atovaquone with trimethoprim/sulfamethoxazole as *Pneumocystis carinii* pneumonia prophylaxis following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 1999; 24:897–902.

39. Torre-Cisneros J, De la Mata M, Pozo JC, et al. Randomized trial of weekly sulfadoxine/pyrimethamine vs. daily low-dose trimethoprim-sulfamethoxazole for the prophylaxis of *Pneumocystis carinii* pneumonia after liver transplantation. Clin Infect Dis 1999; 29:771–4.

40. Souza JP, Boeckh M, Gooley TA, Flowers ME, Crawford SW. High rates of *Pneumocystis carinii* pneumonia in allogeneic blood and marrow transplant recipients receiving dapsone prophylaxis. Clin Infect Dis 1999; 29:1467–71.

41. Vasconcelles MJ, Bernardo MV, King C, Weller EA, Antin JH. Aerosolized pentamidine as *Pneumocystis* prophylaxis after bone marrow transplantation is inferior to other regiments and is associated with decreased survival and an increased risk of other infections. Bio Blood Marrow Trans 2000; 6:35–43.

42. Sepkowitz KA. PCP without AIDS: who should receive prophylaxis? Mayo Clin Proceedings 1996; 71:102–3.

43. Mansharamani NG, Balachandran D, Vernovsky I, Garland R, Koziel H. Peripheral blood CD4$^+$ T-lymphocyte counts during *Pneumocystis carinii* pneumonia in immunocompromised patients without HIV infection. Chest 2000; 118:712–20.

44. Hajjeh RA, Conn LA, Stephens DS, et al. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus–infected persons. J Infect Dis 1999; 179:449–54.

45. Currie BP, Casadevall A. Estimation of the prevalence of cryptococcal infection among patients infected with the human immunodeficiency virus in New York City. Clin Infect Dis 1994; 19:1029–33.

46. Sebti A, Shah MK, Sepkowitz KA. Invasive cryptococcosis in HIV-negative patients at a cancer center [abstract]. In: Proceedings and abstracts of the 11th Annual Focus on Fungus, Washington DC. 2001.

47. Patel R, Portela D, Badley AD, et al. Risk factors of invasive *Candida* and non-*Candida* fungal infections after liver transplantation. Transplantation 1996; 62:926–34.

48. Jabbour N, Reyes J, Kusne S, Martin M, Fung J. Cryptococcal meningitis after liver transplantation. Transplantation 1996; 61:146–9.

49. Singh N, Gayowski T, Wagener MM, Marino IR. Clinical spectrum of invasive cryptococcosis in liver transplant recipients receiving tacrolimus. Clin Transplant 1997; 11:66–70.

50. Horrevorts AM, Huysmans FT, Koopman RJ, Meis JF. Cellulitis as first clinical presentation of disseminated cryptococcosis in renal transplant recipients. Scand J Infect Dis 1994; 26:623–6.

51. White M, Cirrincione C, Blevins A, Armstrong D. Cryptococcal meningitis: outcome in patients with AIDS and patients with neoplastic disease. J Infect Dis 1992; 165:960–3.

52. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. N Engl J Med 1997; 337:15–21.

53. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Clin Infect Dis 2000; 30:710–8.

54. Dromer F, Mathoulin S, Dupont B, et al. Comparison of the efficacy of amphotericin B and fluconazole in the treatment of cryptococcosis in human immunodeficiency virus–negative patients: retrospective analysis of 83 cases. Clin Infect Dis 1996; 22(Suppl 2):S154–60.

55. Chugh KS, Sakhuja V, Jain S, et al. High mortality in systemic fungal infections following renal transplantation in third-world countries. Nephrol Dial Transplant 1993; 8:168–72.

56. Lauerma AI, Jeskanen L, Rantanen T, Stubb S, Kariniemi A. Cryptococcosis during systemic glucocorticosteroid treatment. Dermatology 1999; 199:180–2.

57. Mitchell DH, Sorrell TC, Allworth AM, et al. Cryptococcal disease of the CNS in immunocompetent hosts: influence of cryptococcal variety on clinical manifestations and outcome. Clin Infect Dis 1995; 20:611–6.

58. Moosa MYS, Coovadia YM. Cryptococcal meningitis in Durban, South Africa: a comparison of clinical features, laboratory findings, and outcome for human immunodeficiency virus (HIV)-positive and HIV-negative patients. Clin Infect Dis 1997; 24:131–4.

59. Fujita NK, Reynard M, Sapico FL, Guze LB, Edwards JE. Cryptococcal intracerebral mass lesions. Ann Intern Med 1981; 94:382–8.

60. Peachey PR, Gubbins PO, Martin RE. The association between cryptococcal variety and immunocompetent and immunocompromised hosts. Pharmacotherapy 1998; 18:255–64.

61. Bennett C, Vardiman J, Golomb H. Disseminated atypical mycobacterial infection in patients with hairy cell leukemia. Am J Med 1986; 80:891–6.

62. Akiyama H, Maruyama T, Uetake T, Kawaguchi K, Sakamaki H, Ono-zawa Y. Systemic infection due to atypical mycobacteria in patients with chronic myelogenous leukemia. Rev Infect Dis 1991; 13:815–8.

63. Gaviria JM, Garcia PJ, Garrido SM, Corey L, Boeckh M. Nontuberculous mycobacteria infection in hematopoietic stem cell transplant recipients: characteristics of respiratory and catheter-related infections. Bio Blood Marrow Transplant 2000; 6:361–9.

64. Roy V, Weisdorf D. Mycobacterial infections following bone marrow transplantation: a 20 year retrospective review. Bone Marrow Transplant 1997; 19:467–70.

65. Lichtenstein IH, MacGregor RR. Mycobacterial infections in renal transplant recipients: report of five cases and review of the literature. Rev Infect Dis 1983; 5:216–26.

66. Novick RJ, Moreno-Cabral CE, Stinson EB, et al. Nontuberculous mycobacterial infections in heart transplant recipients: a seventeen-year experience. J Heart Transplant 1990; 9:357–63.

67. Malouf MA, Glanville AR. The spectrum of mycobacterial infection after lung transplantation. Am J Respir Crit Care Med 1999; 160:161–6.

68. Patel R, Roberts G, Keating MR, Paya CV. Infections due to nontuberculous mycobacteria in kidney, heart, and liver transplant recipients. Clin Infect Dis 1994; 19:263–73.

69. Shah M, Sebti A, Kiehn TE, Sepkowitz KA. *Mycobacterium hemophilum* infection at a cancer center. Clin Infect Dis 2001; 33:330–7.

70. Yeager H Jr, Raleigh JW. Pulmonary disease due to *Mycobacterium intracellulare*. Am Rev Respir Dis 1973; 108:547–52.

71. Prince DS, Peterson DD, Steiner RM, et al. Infection with *Mycobacterium avium* complex in patients without predisposing conditions. N Engl J Med 1989; 321:863–8.

72. Ingram CW, Tanner DC, Durack DT, Kernodle GW Jr, Corey GR. Disseminated infection with rapidly growing mycobacteria. Clin Infect Dis 1993; 16:463–71.

73. Levendoglu-Tugal O, Munoz J, Brudnicki A, Ozkaynak MF, Sandoval C, Jayabose S. Infections due to nontuberculous mycobacteria in children with leukemia. Clin Infect Dis 1998; 27:1227–30.

74. Benator DA, Gordin FM. Nontuberculous mycobacteria in patients with human immunodeficiency virus infection. Semin Respir Infect 1996; 11:285–300.

75. Horsburgh CR Jr, Mason UG, Farhi DC, Iseman MD. Disseminated infection with *Mycobacterium avium-intracellulare*. Medicine (Baltimore) 1985; 64:36–48.

76. Jacobson K, Garcia R, Libshitz H, et al. Clinical and radiological features of pulmonary disease caused by rapidly growing mycobacteria in cancer patients. Eur J Clin Microbiol Infect Dis 1998; 17:615–21.

77. Hall CM, Willcox PA, Swanepoel CR, Kahn D, Van Zyl Smit R. Mycobacterial infection in renal transplant recipients. Chest 1994; 106:435–9.

78. Iseman MD. *Mycobacterium avium* complex and the normal host: the other side of the coin. N Engl J Med 1989; 321:896–8.

79. Race EM, Adelson-Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. Lancet 1998; 351:252–5.

80. Mera JR, Whimbey E, Elting L, et al. Cytomegalovirus pneumonia in adult nontransplantation patients with cancer: review of 20 cases occurring from 1964 through 1990. Clin Infect Dis 1996; 22:1046–50.

81. Nichols WG, Boeckh MJ. Recent advances in the therapy and prevention of CMV infections. Clin Virol 2000; 16:25–40.

82. Eddleston M, Peacock S, Juniper M, Warrell DA. Severe cytomegalovirus infection in immunocompetent patients. Clin Infect Dis 1997; 24:52–6.

83. Kanno M, Chandrasekar PH, Bentley G, Vander Heide RS, Alangaden GJ. Disseminated cytomegalovirus disease in hosts without acquired immunodeficiency syndrome and without an organ transplant. Clin Infect Dis 2001; 32:313–6.

84. Ikura Y, Matsuo T, Ogami M, et al. Cytomegalovirus associated pancreatitis in a patient with systemic lupus erythematosus. J Rheumatol 2000; 27:2715–7.

85. Nguyen Q, Estey E, Raad I, et al. Cytomegalovirus pneumonia in adults with leukemia: an emerging problem. Clin Infect Dis 2001; 32:539–45.

86. Cheung AN, Ng IO. Cytomegalovirus infection of the gastrointestinal tract in non-AIDS patients. Am J Gastroenterol 1993; 88:1882–6.

87. Buckner FS, Pomeroy C. Cytomegalovirus disease of the gastrointestinal tract in patients without AIDS. Clin Infect Dis 1993; 17:644–56.

88. Crippa F, Corey L, Chuang EL, Sale G, Boeckh M. Virological, clinical, and ophthalmologic features of cytomegalovirus retinitis after hematopoietic stem cell transplantation. Clin Infect Dis 2001; 32:214–9.

89. Sebti A, Kiehn TE, Sepkowitz KA. CMV disease among cancer patients without established risk: a 3-year retrospective study at MSKCC [abstract 679]. Clin Infect Dis 1999; 29:1081.

90. Ng P, McCluskey P, McCaughan G, Glanville A, MacDonald P, Keogh A. Ocular complications of heart, lung, and liver transplantation. Br J Ophthalmol 1998; 82:423–8.

91. Papanicolaou GA, Meyers BR, Fuchs WS. Infectious ocular complications in orthotopic liver transplant patients. Clin Infect Dis 1997; 24:1172–7.

92. Fishburne BC, Mitrani AA, Davis JL. Cytomegalovirus retinitis after cardiac transplantation. Am J Ophthalmol 1998; 125:104–6.

93. Humar A, O'Rourke K, Lipton J, et al. The clinical utility of CMV surveillance cultures and antigenemia following bone marrow transplantation. Bone Marrow Transplant 1999; 23:45–51.

94. Nguyen Q, Champlin R, Giralt S, et al. Late cytomegalovirus pneumonia in adult allogeneic blood and marrow transplant recipients. Clin Infect Dis 1999; 28:618–23.

95. Slifkin M, Tempesti P, Poutsiaka DD, Snydman DR. Late and atypical cytomegalovirus disease in solid-organ transplant recipients. Clin Infect Dis 2001; 33:E62–8.