9. AIDS IN THE INTENSIVE CARE UNIT

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Introduction

Since Acquired Immunodeficiency Syndrome (AIDS) was first recognized, it has been a leading cause of death among young people in the industrialized world and has had devastating effects in developing nations [1]. With the introduction of modern antiretroviral therapy, there has been a marked decline in the incidence of AIDS among treated Human Immunodeficiency Virus (HIV)-infected individuals. Since 1995, stabilization in the incidence of AIDS-related opportunistic infections in industrialized countries has been followed by a reduction in the rate of new AIDS case and AIDS-related mortality. These changes are thought to be due to the introduction of highly active antiretroviral combination regimens [2–5]. Although the admission rates of HIV-infected persons to the intensive care unit (ICU) are likely to have fallen in conjunction with a decline in the AIDS case-rate, there are no data to substantiate this. Moreover, changes in the rate of HIV infection and demographics of those infected also can be expected to alter the frequency of ICU admission of HIV positive persons [6].

The pandemic of HIV infection is expanding rapidly especially in developing nations [5]. Estimates by the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO), a cosponsor of the Joint Program, indicate that by the beginning of 1998 over 30 million people were infected with HIV, the virus that causes AIDS, and that 11.7 million people around the world had already lost their lives to the disease. Unless a cure is found or life-prolonging therapy can be made more widely available, the majority of those now living with HIV will die within a decade.

These deaths will not be the last; there is worse to come. The virus continues to spread, causing nearly 16,000 new infections a day. During 1997 alone, that meant 5.8 million new HIV infections, despite the fact that more is known now than ever before about how to prevent the spread of the epidemic.

Despite improvements in HIV treatment and access to medical resources in industrialized countries, however, the growth of the epidemic is no less alarming. For example, the rate of new HIV infections almost doubled in Canada between 1992 and 1996 with an increase in infection rates among women, aboriginal peoples and injection drug users. There has been increasing heterosexual transmission of HIV among minorities in the United States, while the incidence of infection has fallen among homosexual men and injection drug users [6]. In Europe, injection drug use accounts for 40% of cases of HIV infection and there have been explosive outbreaks in this population in Eastern Europe [7]. HIV infection is now considered virtually endemic in the United States [8].

Hence, the rate of HIV infection is rising particularly among groups with less access to medical care. Use of opportunistic infection prophylaxis and antiretroviral therapy by individuals in these groups is less likely: their presentation with advanced HIV disease and its complications therefore should be anticipated

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[6]. Hence, just as AIDS will not disappear even with the advent of effective antiretroviral regimens, so too is it likely that AIDS-related complications will continue to be encountered in the ICU.

Human Immunodeficiency Virus Infection

VIROLOGY AND COURSE OF INFECTION

AIDS is caused by chronic infection with the lentivirus HIV, which is a member of the family of retroviruses. The virus infects cells principally by binding to the CD4 molecule, a cell surface glycoprotein which acts as receptor for the major histocompatibility (MHC) II molecule, although binding to a chemokine coreceptor is also necessary for viral entry into the cell [9, 10]. Hence, HIV primarily infects cells bearing a CD4 receptor: helper T-lymphocytes and monocytes/macrophages. However, HIV can also infect cells which do not bear the CD4 receptor, including gastrointestinal and cervical mucosal cells, megakaryocytes, renal epithelial cells, cardiac myocytes and neurons, although the clinical significance of this property is unclear [11].

After the virus enters the cell, reverse transcription of the viral ribonucleic acid (RNA) genome occurs by means of a reverse transcriptase contained within the virus, producing pro-viral double-stranded deoxyribonucleic acid (DNA). The DNA particles gain access to the nucleus and are generally integrated into the host genome, where they enter a state of latency. With activation of the cell (such as during an immune response to intercurrent infection), transcription of proviral DNA is initiated and viral RNA and proteins are synthesized. New virions are assembled and bud from the cell, thus spreading infection to other susceptible cells [12] (see Figure 1).

Chronic infection with HIV results in gradual destruction of CD4+ (helper) T-lymphocytes with progressive immune deterioration, culminating in the clinical syndrome of opportunistic infections and malignancies characterizing AIDS. The mechanism of immune destruction is complex and involves both direct HIV-mediated cytopathic effects (such as destruction of individual cells and formation of syncytia) and indirect, nonvirologic mechanisms (reviewed in detail in [10]). The latter include the action of HIV as a superantigen (thus stimulating the T-cell receptor directly); induction of an autoimmune response due to the similarity of HIV to the MHC molecule; stimulation of apoptosis (programmed cell death); and virus-specific cytotoxic immune responses [9, 10].

The clinical course of HIV infection has been delineated clearly [9, 10, 13] (see Figure 2). Approximately 1–6 weeks after primary infection with HIV, 50–70% of patients suffer an acute mononucleosis-like syndrome, often with a rash, but usually the syndrome is not recognized (or only identified retrospectively). During this benign, self-limited seroconversion illness, there is a high level of viremia followed by a cellular and humoral immune response against HIV, which is established within one week to three months of infection. With the establishment of immunity, the level of viremia usually declines. However, the immune response is inadequate to eradicate or contain the infection, and viral replication persists. Even if viremia is undetectable, HIV replication continues unabated in lymphoid tissue.

After initial infection, most patients enter a period of clinical latency for several years (generally 8–12 years, variable with age at seroconversion [14]). Most patients remain asymptomatic or suffer only minor symptoms (such as persistent generalized lymphadenopathy) during this time, but viral replication and destruction of the immune system progress relentlessly with eventual collapse off CD4+ T-lymphocyte number and function. Profound immunosuppression ensues with the development of persistent constitutional symptoms, opportunistic infections and neoplasms typical of the end-stage of HIV infection (AIDS; Figure 2).

The rapidity of immune destruction and hence prognosis in HIV infection is clearly

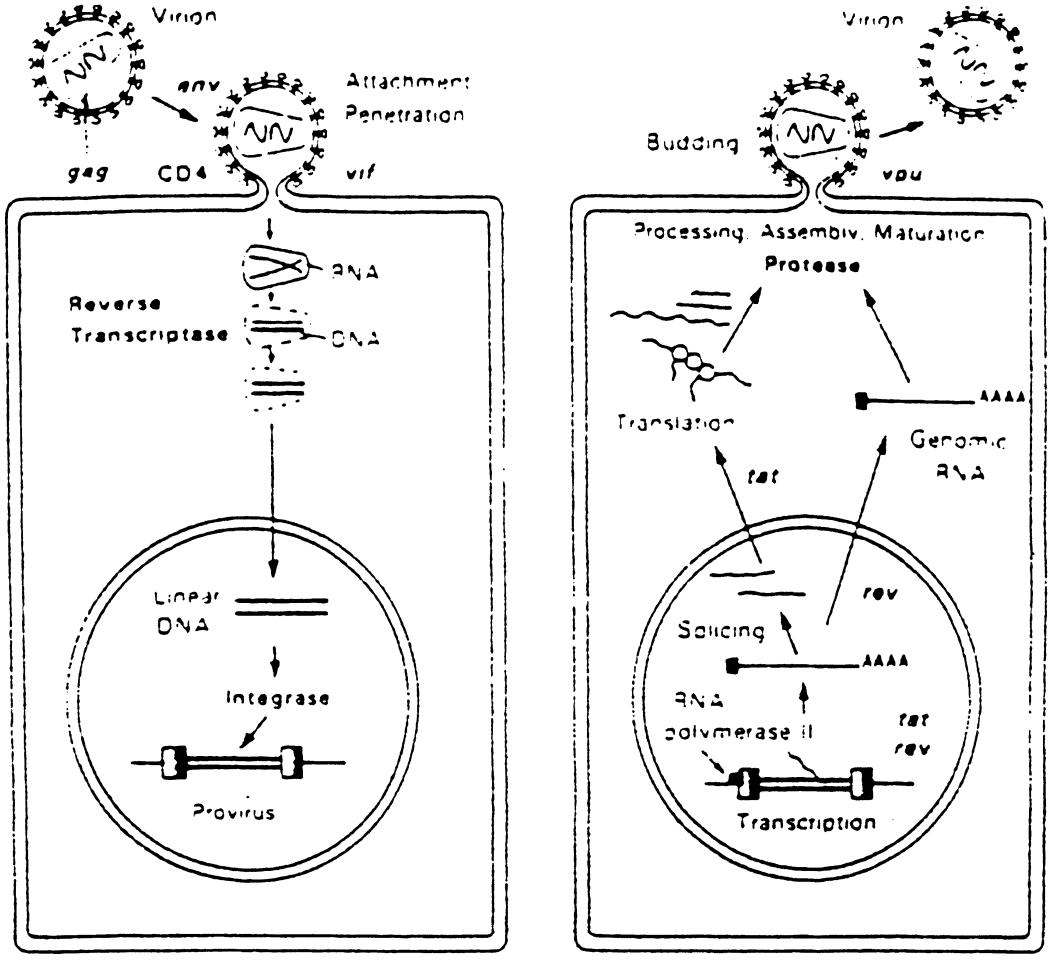


FIGURE 1. The life cycle of the human immunodeficiency virus. (Reproduced with permission from Blattner *et al.* (93).)

linked to the level of viremia as assessed by the plasma viral load [15] (Figure 3). Most untreated patients (approximately 80%) progress to AIDS in 8–12 years. In some (<10%), immune destruction does not progress for an extended period; such patients are characterized by stable, normal CD4+ counts and low plasma viral load, likely the consequence of a more enhanced immune response to HIV infection. Others (1–15%) progress much more rapidly (within 2–3 years) and are typified by a high plasma viral load and lower levels of anti-HIV antibodies. Hence, the natural history of HIV infection is heterogeneous [10]. Ultimately, though, HIV infection carries a 100% mortality rate.

ANTIRETROVIRAL THERAPY

The course of the disease has been altered substantially by the advent of highly active combination antiretroviral therapy (usually with three or more agents) which has been able to reduce plasma viral loads in infected individuals to undetectable levels [16]. Such potent antiviral effects have been associated with increases in CD4+ T-lymphocyte counts, immune reconstitution and reduction in the incidence of AIDS-

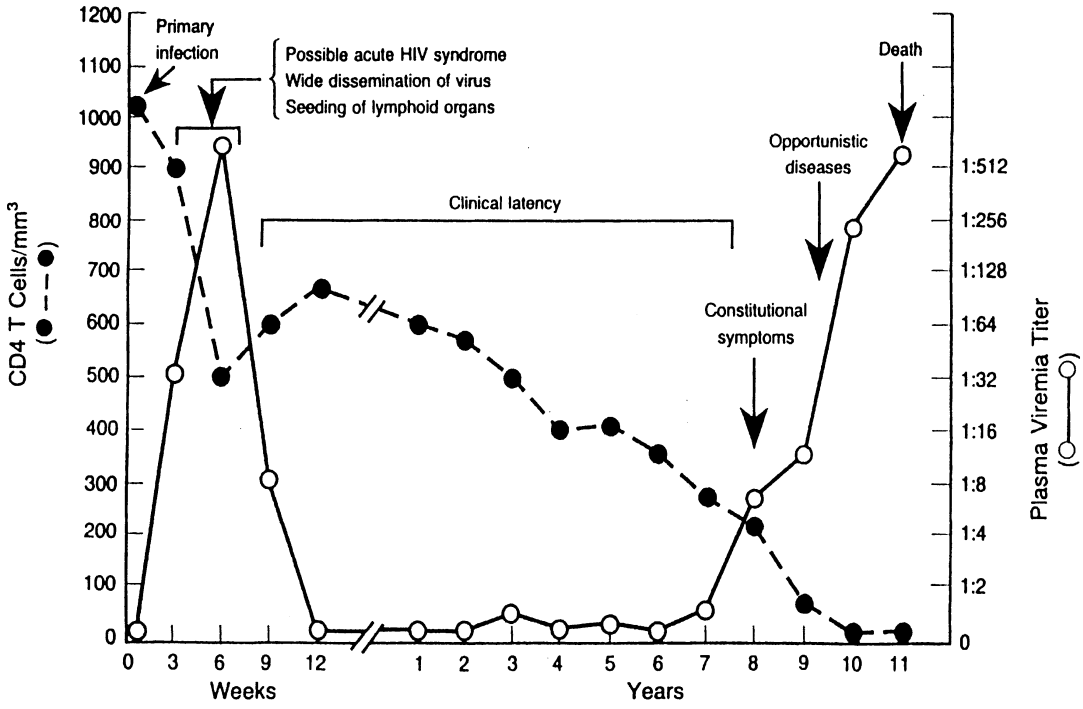


FIGURE 2. The natural history of HIV infection. During the early period of infection, there is widespread dissemination of virus and a sharp decline in the number of CD4+ cells in peripheral blood. An immune response to HIV ensues, with a decrease in detectable viremia followed by prolonged clinical latency. The CD4+ count continues to decrease during subsequent years, until it reaches a critical level, below which there is significant immunocompromise and a substantial risk of opportunistic infections and malignancies characteristic of AIDS. (Reproduced with permission from Pantaleo *et al.* (9).)

defining illnesses among HIV-positive persons and decreased mortality due to AIDS [2–5, 16, 17]. However, initial hope that this might herald a cure for HIV infection has not been realized [16].

The many antiretroviral drugs now available have significant adverse effects and many drug interactions, compounded by their use in combination. Critical care practitioners require an understanding of the potential effects of these agents (*vide infra*). In view of these toxicities, it is generally unwise to initiate combination antiretroviral therapy in critically ill patients. Further, many of the antiretroviral agents are difficult to administer in the critical care setting: some must be taken with food or without, they may be difficult to administer via a nasogastric tube and there are many potential interactions with other medications required in the setting of the acute illness. Thus, although the development of an AIDS-defining illness in a patient naïve to antiretroviral therapy is a clear indication for its institution, usually this should be delayed until the critical illness has resolved.

HIV replication, plasma viral load and destruction of the immune system rebound immediately following discontinuation of antiretroviral therapy [16, 17]. It is reasonable, then, to continue preexisting therapy, provided there are no adverse effects of the agents used which may result in further compromise of the patient's condition and it is possible to administer them. On the other hand, if the reason for admission to ICU is an AIDS-defining illness despite patient

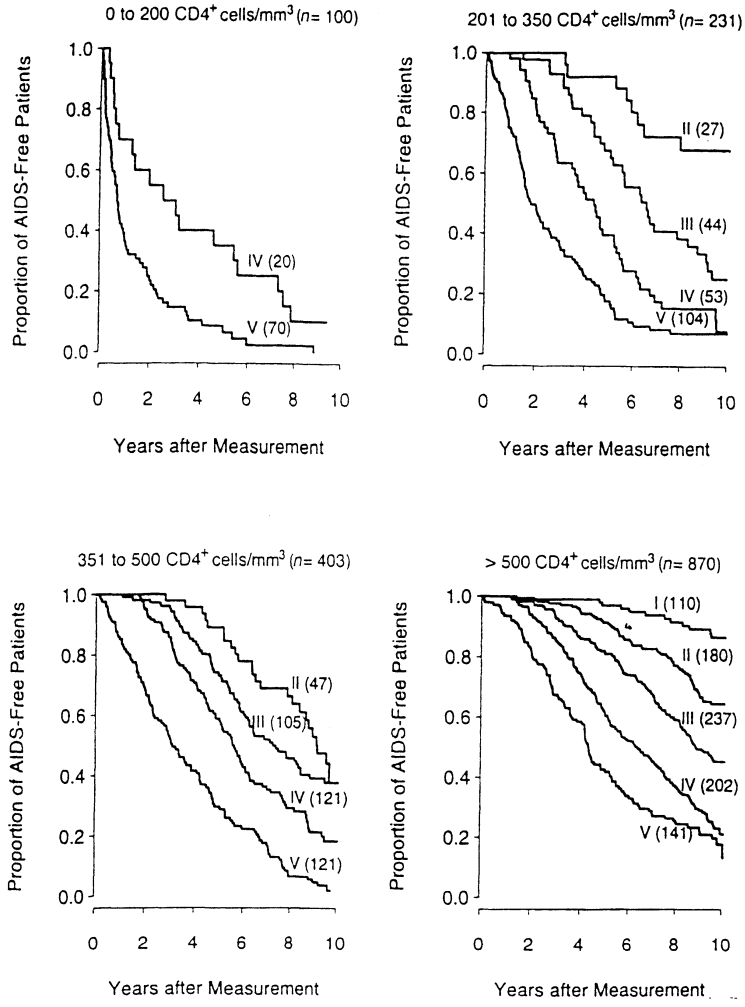


FIGURE 3. Plasma viral load and prognosis in HIV-1 infection. Kaplan-Meier curves showing AIDS-free survival by HIV-1 RNA viral load category among groups with different baseline CD4+ lymphocyte counts. The five categories of HIV-1 RNA were the following: I = 500 copies/mL; II = 501-3000 copies/mL; III = 3001-10000 copies/mL; IV = 10001-30000 copies/mL; V = > 30000 copies/mL. (Reproduced with permission from Mellors *et al.* (15).)

adherence for at least several weeks to the regimen prescribed, it is likely the regimen is ineffective and its continuation will not be beneficial. In any case, whenever antiretroviral therapy is discontinued, *it is imperative that all agents be stopped.* Even temporary interruption of one of the antiretroviral agents in a multi-drug regimen risks induction of viral resistance and can seriously compromise future antiretroviral management [16]. Consultation with a physician who specializes in HIV care and is familiar with antiretroviral agents is recommended.

SURROGATE MARKERS IN HIV INFECTION

A number of laboratory tests correlate with HIV disease prognosis and are called *surrogate markers* of disease progression. Of these, the most important for modern management of the HIV-

positive patient are the plasma viral load and the CD4+ T-lymphocyte count [16]. The prognostic value of the former has been demonstrated [15] (Figure 3): since it provides evidence of the level of viral replication, its use primarily is related to monitoring virologic response to antiretroviral therapy [16].

HIV plasma viral load is a measure of circulating viral RNA by polymerase chain reaction (PCR). A low level of circulating HIV RNA implies a lower level of viral reproduction in lymphoid tissue and correspondingly less aggressive immune destruction. Thus, a low HIV plasma viral load portends slower progression of HIV disease and a better prognosis. The median survival of untreated individuals with a plasma viral load less than 5000 copies per ml is 10 years. On the other hand, a high viral load indicates unchecked HIV replication and aggressive destruction of the immune system. HIV-positive individuals with high viral loads have a poorer prognosis; untreated patients with a plasma viral load in excess of 34,000 copies per ml have a median survival of three years [15]. These observations have been confirmed in clinical trials of antiretroviral therapy, which have also shown that plasma viral load is predictive of survival independent of the CD4+ T-lymphocyte count [16].

The primary goal of highly active antiretroviral therapy is to reduce viral replication (as reflected by the plasma viral load) to the lowest level possible, thereby delaying immune system deterioration. By so doing, a second goal of therapy can also be achieved, namely the limitation of emerging viral resistance to antiretroviral agents, since suppression of viral replication limits the opportunity for resistant mutations to occur.

Hence, in the ideal situation, plasma viral load is reduced to levels reported as "undetectable". This does not mean, however, that viral replication, disease activity and thus immune destruction are completely suppressed: viral RNA is simply no longer measurable in the plasma. Detection of circulating viral RNA is dependent on the sensitivity of the assay used and the lowest identifiable level of viral RNA in plasma [18, 19]. More importantly, viral replication may continue in "sequestered sites" within the lymphoid system, even in the complete absence of plasma viral RNA. Indeed, immunologic benefits of antiretroviral agents may reflect more the result of inhibition of viral activity and thus reduced suppression of various mechanisms of nonvirologic immune destruction than their reduction of HIV burden *per se* [17]. Although useful as a tool for monitoring response to antiviral treatment of HIV infection, the plasma viral load therefore has a number of limitations and has no prognostic or diagnostic utility in the ICU setting.

While the HIV plasma viral load is indicative of the level of viral activity and rapidity of destruction of the immune system, the more traditional surrogate marker, the CD4+ T-lymphocyte count, provides evidence of the degree of immunosuppression resulting from HIV infection. Hence, a low number of CD4+ cells corresponds to susceptibility of the HIV-infected individual to opportunistic infections and neoplasms that occur once HIV-induced immune destruction has progressed to its final stage (AIDS) [20]. The CD4+ T-lymphocyte count has been demonstrated to be a useful prognostic marker and therapeutic endpoint in multiple studies [16]. It also serves as an important criterion for staging of HIV infection, for recommendations regarding initiation and goals of therapy, and for institution of prophylaxis against opportunistic infections in HIV disease [1, 16].

The CD4+ count can be measured in traditional units (number of CD4+ cells per microliter) or in metric units (number of CD4+ cells $\times 10^9$ per liter). Thus, for instance, a CD4+ count of 500/μl in traditional units is equal to 0.5×10^9/l in metric units. By convention, however, traditional units have become the standard used. The normal CD4+ count is 400–1400 cells/μl. HIV-positive individuals are at risk of AIDS-related complications at a CD4+ count

less than 250 cells/μl and CD4+ count less than 200 cells/μl is now considered consistent with a diagnosis of AIDS in the revised CDC classification (1993) [13]. It is important to consider not just the absolute number of CD4+ cells, but also their number in relation to the total circulating pool of T-lymphocytes. This is usually reported as a fraction or percentage of the total lymphocyte count. Generally, a CD4+ fraction less than 15% suggests significant immunosuppression and may reflect susceptibility to AIDS-defining opportunistic infections, even at an absolute CD4+ count which otherwise would not be considered indicative of such immune dysfunction.

Despite the widespread acceptance of the CD4+ count as a guide to decision making in HIV care and a reflector of immune dysfunction, there are several problems with its use in the acute setting. First, there is considerable diurnal variability in CD4+ lymphocyte counts, even in non-HIV-infected persons: CD4+ counts show circadian variation with counts being lowest in the morning and highest in the evening. This effect is less pronounced in HIV-infected individuals than in healthy ones. While consistent measurement of CD4+ count at a fixed point in the day can limit this variability in the ambulatory setting [16], loss of normal circadian rhythm in the critically ill make the effect of such fluctuations throughout the day impossible to determine in the individual patient.

The CD4+ count can also vary from day to day, so that short-term fluctuations in CD4+ count of up to 30% may occur which are not attributable to a change in disease status [20]. Therefore, it is recommended that at least two measurements be made of CD4+ count on different days in order to better assess the actual state of immune function [16]. Given the daily perturbations in the critically ill population in organ system function, including fluctuations in immune system function, it is not clear that repeated measurements of CD4+ count in a critically ill patient will enhance its predictability of the degree of immunosuppression.

Finally, the CD4+ count can vary with immune stimulation, such as with intercurrent illness. For example, in a non-HIV-infected individual, severe viral infection can cause marked depression of CD4+ count, even to levels indicative of profound immunosuppression in an HIV-infected patient. Yet such depression of CD4+ cell number does not correlate with enhanced susceptibility to the opportunistic infections characteristic of AIDS. Similarly, fluctuations of CD4+ count in an acutely ill HIV-positive individual may also occur regardless of cause and may not be reflective of actual level of immune dysfunction [20].

For these reasons, a CD4+ count (even if repeated) should not be regarded as a reliable indicator of immunosuppression in the critically ill patient. In other words, predicting the likelihood of HIV-related illness in a critically ill patient (regardless of HIV status) on the basis of a low CD4+ T-lymphocyte count (absolute and/or relative) is not dependable. In contrast, a high or normal CD4+ count (i.e., >250 cells/μl) and CD4+ fraction greater than 15% suggest that HIV-related illness is unlikely. Regardless, the most reliable reflector of immune function is a CD4+ count a short time prior to the onset of the presenting illness and such information should be sought. Furthermore, diagnostic and therapeutic decisions should not be driven by the CD4+ count alone. Hence, we feel there is only a limited rôle for CD4+ counts in the critical care setting.

It should be noted that the description of HIV plasma viral load as a marker of viral activity and the CD4+ T-lymphocyte count as a marker of degree of immunosuppression is clearly an oversimplification. The virology and immunopathology of HIV infection is increasingly recognized as complex and is still incompletely understood [10, 17]. There are qualitative defects in lymphocyte function and other aspects of immune function in HIV disease not reflected by the absolute or relative CD4+ T-lymphocyte count. Furthermore, the level of plasma HIV RNA does not precisely reflect the immunopathologic

effects of HIV infection. The immunologic responses to antiretroviral therapy in HIV infection demonstrate the complex interactions between viral activity and immune changes in HIV disease [17]. For example, disease activity and immune dysfunction can persist even in the presence of apparent suppression of viral replication; increases in CD4+ counts may not correspond to repair of immune dysfunction and initial increases in CD4+ levels may be associated with exacerbation or development of opportunistic infections. Immunologic and clinical benefits have been observed using antiretroviral regimens which are no longer able to suppress plasma viral load. Thus, the plasma viral load and CD4+ count should preferably be considered as surrogate markers and are imperfect indicators of disease activity and progression.

Spectrum of HIV-Related Disease in the ICU

There are relatively few conditions which lead to ICU admission among HIV seropositive persons. Causes of ICU admission unrelated to HIV infection are similar to those among non-HIV-infected individuals of similar age and demographics. Furthermore, since HIV infection is asymptomatic early in its course when there is relatively normal immune function, patients with unsuspected HIV infection may develop non-HIV-related illness which may require admission to ICU. Given the changing demographics of HIV infection, admission of HIV-positive patients with non-HIV-related critical illness typical of HIV-negative persons with similar risk factors for HIV infection (such as endocarditis, pneumonia and soft tissue infections in injection drug users) is likely to become more common. In addition, as antiretroviral therapies improve and longevity and preservation of immune function increase, it should be anticipated that more HIV-positive patients will be admitted to ICU with illnesses associated with disease found in non-HIV-infected persons. Patients with critical illness not connected to underlying HIV infection have a prognosis similar to individuals without HIV infection who have the same illness and such patients usually respond similarly to management for their condition [20].

It is not clear that the spectrum of HIV-related critical illness has changed from that found in previous years [20]. Recent studies, for example, suggest that *Pneumocystis carinii* pneumonia (PCP) is less prevalent, constituting only 16–27% of admissions [6, 21]. However, these studies were based on data collected prior to 1993 and the modern era of antiretroviral therapy and/or included patients either with low acuity illness (e.g., uncomplicated pneumothorax) or non-AIDS complications (e.g., ischemic heart disease, drug overdose or trauma). Nevertheless, the study by Casalino *et al.* from an Infectious Diseases ICU in a French hospital is instructive [21]. Not surprisingly, 33.5% of admissions to the ICU in the period studied (1990–1992) were HIV-related. Of the 354 patients evaluated, 49% were admitted with respiratory failure (45% of whom were admitted because of PCP; other causes of respiratory failure included bacterial pneumonia (47%), tuberculosis, Kaposi's sarcoma and toxoplasmic pneumonia); 27% of patients had neurologic complications (predominantly toxoplasmic encephalitis (62%), but also meningitis (17%) and other cerebral lesions); 10% had severe sepsis (primarily related to bacteremia or bacterial pneumonia); 5% were admitted with cardiac dysfunction due to opportunistic infection and complications, such as pericarditis, or HIV-related dilated cardiomyopathy, and 9% were admitted for "miscellaneous" reasons, most not directly related to HIV disease, such as drug overdoses and toxic drug reactions. Although this implies a broad spectrum of HIV-related disease in the ICU, the specialization of the ICU in this study as a referral center for critically ill patients with infectious diseases may not be representative of more general systems or even medical ICUs.

In contrast, most studies have shown that PCP is the predominant cause of HIV-related acute respiratory failure (ARF), accounting for 63–93% of admission to the ICU among HIV seropositive patients [6], although this is based again on observations prior to the modern era of HIV treatment. Recent data suggest that the spectrum of AIDS defining illnesses in HIV seropositive patients treated with highly active antiretroviral therapy has not changed and that PCP remains the most common AIDS defining illness in this group (Figure 4) [22]. Finally, combination antiretroviral therapy is associated with reconstitution of immune function [17], with increasingly common recommendations that PCP prophylaxis can be stopped in individuals who have improved CD4+ counts [23]. If indeed immune reconstitution is not sufficient to provide protection against AIDS complications and/or such immune recovery is not sustained, even those patients on highly active antiretroviral therapy may be at risk for development of opportunistic infections. Hence, PCP is likely to remain a common AIDS-related complication precipitating admission to the ICU.

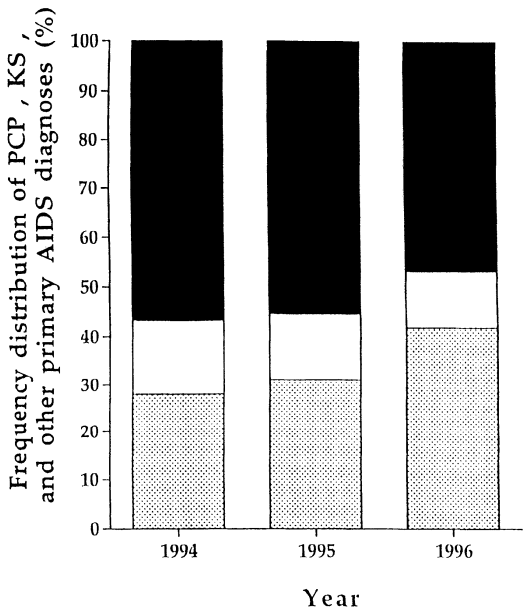


FIGURE 4. Proportion of AIDS index diseases attributed to *Pneumocystis carinii* pneumonia (PCP; gray bar), Kaposi's sarcoma (KS; white bar) and other AIDS-defining illnesses (black bar) among participants in a drug treatment program ever prescribed antiretroviral therapy between January 1, 1994 and December 31, 1996. There was no significant difference in the proportion of patients who developed AIDS due to PCP ($p = 0.048$ for 1994 versus 1996), Kaposi's sarcoma ($p = 0.442$ for 1994 versus 1996) or Other AIDS-defining illness ($p = 0.190$ for 1994 versus 1996). (Reproduced with permission from Forrest *et al.* (22).)

While HIV infection is a multisystem disease and the manifestations of HIV-related immune dysfunction involve multiple organ systems, complications of HIV infection relevant to the intensivist will be discussed according to organ system.

Respiratory Disease

APPROACH

While PCP remains the most frequent cause of acute respiratory failure in HIV seropositive individuals, there is a broad differential diagnosis which should be considered. The differential diagnosis includes bacterial pneumonia (e.g., community acquired pneumonia, atypical pneumonia and mycobacterial infection), fungi, viruses, parasites (such as *Toxoplasma*), and non-infectious etiologies, such as lymphocytic interstitial pneumonitis and neoplastic diseases (Table 1). Following hospital admission, the diagnosis of nosocomial pneumonia should be considered. Occasionally multiple etiologies can coexist (e.g., pneumococcal infection complicating PCP).

There are no specific clinical clues which can differentiate these various causes of respiratory failure. There is sufficient overlap of clinical, radiological and laboratory findings that it is difficult to make a precise diagnosis without definitive evidence of a specific etiology. However, there are several findings which may be helpful. For example, a CD4+ count, preferably obtained

TABLE 1. Differential diagnosis of pulmonary complications of HIV disease

- Infections
  - Bacteria
    - *Streptococcus pneumoniae*
    - *Hemophilus influenzae*
    - *Staphylococcus aureus*
    - *Moraxella catarrhalis*
    - *Mycobacterium tuberculosis*
    - *Mycobacterium avium* complex
    - Other nontuberculous mycobacteria
    - *Rhodococcus equi*
    - *Nocardia asteroides*
  - Fungi
    - *Pneumocystis carinii*
    - *Cryptococcus neoformans*
    - *Histoplasma capsulatum*
    - *Aspergillus fumigatus*
    - *Blastomyces dernmatitidis*
  - Protozoa
    - *Strongyloides stercoralis*
    - *Toxoplasma gondii*
  - Viruses
    - Cytomegalovirus
    - Herpes simplex
    - Varicella-zoster
    - Adenovirus
    - Other respiratory viruses
- Noninfectious
  - Malignancies
    - Kaposi's sarcoma
    - Non-Hodgkin's lymphoma
    - Primary lung carcinoma
  - Other pulmonary syndromes
    - Lymphocytic interstitial pneumonitis
    - Nonspecific interstitial pneumonitis
    - Bronchiolitis obliterans and organizing pneumonia
    - Primary pulmonary hypertension

Adapted with permission from [63].

shortly before the presenting illness (*vide supra*), can be of value [24]. If the recent CD4+ T-lymphocyte count is >250 cell/μl, an AIDS-defining illness such as PCP is unlikely. A low CD4+ count is not helpful in ruling out any etiology.

Similarly, the level of lactate dehydrogenase (LDH) can assist in differential diagnosis [24, 25]. The serum LDH level is characteristically elevated in an HIV-positive patient with PCP; the degree of increase tends to correlate with th severity of disease and radiographic change, an changes in the LDH level tend to parallel th course of PCP. Hence, a normal LDH level make PCP an unlikely diagnosis. However, an elevate LDH level is not diagnostic, because serum LDH can be raised by other causes of respiratory illnes and non-respiratory disease, such as pulmonar embolism, lymphoma, liver disease or dysfunc tion (a common finding in the critically il population), megaloblastic anemia, hemolysis (a may occur, for example, in HIV-positive patient receiving dapsone) or with various HIV therapie (e.g., antiretroviral medications) [24, 25] Extreme elevations in LDH are less likely to b due to PCP and more likely to indicate anothe diagnosis such as disseminated histoplasmosis disseminated toxoplasmosis, lymphoma, o major hemolysis.

A chest X-ray can provide useful diagnostic clues to etiology [24]. Often at the time o ICU admission, the chest X-ray shows non-specific diffuse pulmonary infiltrate consistent with adult respiratory distress syndrome (ARDS). However, when reviewed retrospectively, the evolution of chest X-ray findings through the course of presenting illness prior to development of respiratory failure can aid in differential diagnosis (see Table 2). The extent of chest radiographic involvement more clearly distinguishes PCP from other causes of pulmonary infiltrate than does the LDH level [25]. Patients who have community acquired bacterial pneumonia will usually have typical signs of asymmetrical, lobar or nonlobar consolidation. Patients who have atypical pneumonia usually have fairly extensive, more symmetric lung involvement that may be out of proportion to clinical signs and symptoms.

It should be emphasized that no finding is sufficiently specific to establish a diagnosis. Hence, definitive determination of the etiology of respiratory failure in the HIV seropositive patient is dependent on the recovery of the causative pathogen and/or histopathologic confirmation [24]. This is especially important when the serostatus of the patient is unknown,

TABLE 2. Major radiologic differential diagnosis of pulmonary involvement in the HIV-positive patient

Chest radiograph appearance	Differential diagnosis
Normal chest X-ray	PCP, CMV, MAC
Diffuse or localized interstitial pattern	PCP, TB, CMV
Diffuse alveolar pattern	PCP, cardiogenic pulmonary edema
Miliary pattern	TB, histoplasmosis
Consolidation	Bacteria, TB, PCP, KS
Nodular opacification	PCP, bacteria, KS, cryptococcosis
Upper lung field predominance	PCP, TB
Cavitary lesions	TB, aspergillosis, PCP, bacteria
Pleural effusion	KS, bacteria, mycobacteria
Pneumothorax	PCP

Abbreviations: PCP = *Pneumocystis carinii* pneumonia; CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex; TB = *Mycobacterium tuberculososis*; KS = Kaposi's sarcoma.
Reproduced with permission from [20].

but also when an HIV-positive patient is not known to have AIDS, because of the serious prognostic and therapeutic implications of a diagnosis of AIDS. Thus, diagnostic investigation should include microbiologic evaluation of tracheobronchial secretions for common bacterial pathogens and mycobacteria and of bronchoscopically obtained specimens (bronchoaveolar lavage and bronchoscopic brush specimens) for bacteria (including *Legionella* and mycobacteria), fungi, *Pneumocystis*, viruses and cytology [24, 26]. Examination for *Pneumocystis* should be requested specifically, as many laboratories do not screen bronchoscopic specimens for this organism routinely. Induction of sputum can increase the sensitivity of noninvasive evaluation for *Pneumocystis* to as high as 94% [27], but its success is highly dependent on the experience of the personnel and laboratory.

Where feasible and with appropriate precautions, bronchoscopy is the preferred diagnostic approach [24, 26] and should certainly be performed if PCP is possible and routine and/or induced sputum examination is negative [27]. Ideally, bronchoscopy should be undertaken prior to institution of empiric therapy. However, as with many other critical infectious illnesses, delay in institution of treatment in favor of a diagnostic procedure is usually not warranted. Nevertheless, even several days of empiric therapy has substantial influence on diagnostic yield of bronchoalveolar lavage (BAL) in HIV-positive persons [28]. Bronchoscopy thus should be performed as soon as possible after institution of treatment, unless a definitive diagnosis is established by other means [26]. Specimens are obtained most easily from the middle lobe, but sampling from the upper lobe has higher yield in patients receiving anti-*Pneumocystis* prophylaxis with aerosolized pentamidine [29].

The sensitivity of BAL for *P. carinii* and other treatable pathogens in the HIV-infected patient is 85–95% [24, 26]; sensitivity can be enhanced by concentrating the specimens [24]. If a definitive etiology is not established by this means, open-lung biopsy may be considered, taking into account the inherent risks and benefits of doing so in the individual case. In our experience, open lung biopsy is rarely necessary. Although transbronchial biopsy can increase the sensitivity of bronchoscopic examination, the complications of the procedure generally render it too risky in the critically ill patient with respiratory failure, particularly if the patient is supported by positive pressure ventilation [20, 26]. Finally, detection of alveolitis (presence of inflammatory cells) and number of CD4+ cells on BAL is predictive of long-term survival in the HIV-seropositive patient, regardless of underlying pulmonary disease [30].

PNEUMOCYSTIS CARINII PNEUMONIA

Based on molecular genetic data, *Pneumocystis carinii* is classified as a fungus [31]. Since *Pneumocystis* cannot be grown in the laboratory, its microbiology is not well understood and *in vitro* antimicrobial sensitivity is thus not possible [32]. The organism is ubiquitous and most healthy children have been infected by *Pneumocystis* at an early age. The organism is distributed worldwide and infects multiple mammalian

species, although there are geographic variations in its prevalence and there seems to be no transmission of infection between species; it is not clear whether there is an environmental reservoir [32]. Nevertheless, such differences in prevalence of the microbes are not sufficient to account for differences in the frequency of infection in immunocompromised hosts: this seems more related to the prevalence of more virulent infections (such as tuberculosis), differences in public health and medical system infrastructure, and lack of access to sophisticated medical care [33].

Animal studies suggest that *Pneumocystis* is transmissible by the airborne route, but clearly the organism poses a risk of clinically significant infection only among immunocompromised hosts with impairment of cellular immunity [33]. Indeed, it is likely that most people are exposed frequently throughout their lives; it is thought that *Pneumocystis* may become part of the host's residential microbial flora or infection may be transient but repetitive. It has been theorized that clinical PCP disease in an immunocompromised host results from reactivation of latent infection, but primary or recurrent infection has been documented as an etiology of PCP in HIV-infected persons and may be much more important than earlier recognized [31, 32, 34, 35]. Although there have been no recommendations to date to isolate patients with PCP, given the risk of transmission and the potential role of primary or recurrent infection in producing clinically significant disease, it may be prudent to consider isolation of patients with PCP from other individuals with compromised cellular immunity [31, 34, 35]. In the setting of HIV infection, PCP occurs as a complication of late-stage HIV disease once the CD4+ count has declined below 200 cells/μl.

The site of primary infection with *Pneumocystis* is the lung, where the organism attaches to alveolar type I cells and maintains an extracellular existence within the alveoli. With immunocompromise, *Pneumocystis* organisms proliferate and fill alveolar spaces forming a foamy alveolar exudate. Damage to type I alveolar cells occurs with increased alveolocapillary permeability and hyaline membrane formation with interstitial fibrosis and edema. Changes in the surfactant system occur with a fall in surfactant phospholipids and a rise in surfactant protein; these alterations likely contribute significantly to the alterations in respiratory function in PCP [32, 33].

The host inflammatory response is manifested by proliferation of type II alveolar cells and a scanty mononuclear infiltrate. Comparative histologic data suggest there may be a higher burden of microbes but less tissue damage in HIV-related pneumocystosis than in PCP occurring in non-HIV-infected hosts [33]. Nevertheless, in the setting of HIV infection, the host response seems more complex and potentially harmful and parenchymal injury actually may worsen with therapy [36]. Inflammation, interstitial edema and fibrosis, type II pneumocyte proliferation and cellular infiltration of the alveolar wall are more abundant than in other HIV-related pulmonary diseases [37].

Typically, PCP has an insidious onset in the HIV-infected host with a two- to three-week prodrome consisting of fever, dyspnea and cough (usually described as nonproductive), in contrast to a more fulminant presentation in other immunocompromised individuals [32]. Chills, weight loss, sputum production, chest pain and hemoptysis have also been described and 6–7% of patients report no symptoms. Adventitious breath sounds are heard in only 30–46%. Clinical presentation does not seem to be altered by type of prophylaxis (if any) used prior to development of PCP [32]. With the use of aerosol pentamidine in the late 1980s and early 1990s, extrapulmonary infection with *Pneumocystis* became increasingly recognized. Virtually any organ can be affected, most frequently lymphatic tissue (including spleen), bone marrow, liver, pancreas and gastrointestinal tract, adrenal, thyroid, parathyroid and pituitary glands, genitourinary system, heart, and the eyes and ears [32].

Routine laboratory testing of PCP is nonspecific; the value of the LDH level is discussed

above. The hallmark of PCP in a predisposed individual is hypoxemia at rest or with exercise out of proportion to the changes found on clinical examination and on chest radiograph. Arterial hypoxemia may not be apparent at rest, but only with exercise, and continuous pulse oximetry has been shown to be useful in this regard [32]. Arterial blood gas measurements may also show respiratory alkalosis; a decline in pH with an inadequate respiratory compensation (manifest by a rising $PaCO_2$ on serial blood gas measurements) suggests respiratory fatigue and incipient respiratory failure.

There are a variety of chest radiograph findings with PCP [32] (Table 2). Indeed, it is prudent to consider PCP with virtually *any* abnormal radiographic findings in the correct clinical setting, but a normal chest X-ray does not rule out PCP. In early stages in non-critically ill patients, normal chest radiographs are found in up to one third of cases. In approximately 80% of established cases, a "classic" appearance is found of ground-glass perihilar interstitial infiltrates progressing over time to involve all lung fields diffusely, often with an alveolar pattern – consistent with findings typical of ARDS. Pleural disease, vascular engorgement, and asymmetric lobar consolidation are unusual. The use of aerosolized pentamidine as prophylaxis has been associated with an increased incidence of upper lobe infiltrates. Cystic changes can also be seen and are usually apical and subpleural. They are more common in patients previously treated prophylactically with aerosolized pentamidine and are most readily detected on computerized tomographic (CT) scanning of the chest. Pulmonary cystic changes also predispose to the development of pneumothoraces, seen in up to 9% of patients. Pneumothorax has been associated with a poor prognosis and tension pneumothorax with cardiopulmonary arrest has been reported. Rarely, transudative or exudative pleural effusions may be found; these resolve spontaneously with treatment of underlying PCP [32, 38].

Nuclear medicine gallium-67 lung scans may also be a useful adjunctive diagnostic modality with a sensitivity of 94–100% but specificity of only 47–74% [32]. However, they are expensive, time-consuming, may not be readily available, and may require movement and transfer of the patient with attendant risks. Because of the lack of diagnostic specificity, this test has limited utility in the critically ill population.

Acute respiratory failure occurs in 5–30% of cases of AIDS-related PCP [39]. Physiologically, acute respiratory failure complicating PCP is similar to that of ARDS with tachypnea, ventilation-perfusion imbalance, hypoxemia, hyperventilation with low pCO_2, and decreased pulmonary compliance. In association, there is a hemodynamic profile typical of a systemic inflammatory response with high cardiac output and distributive shock [32]. End-organ failure and even death may result from direct involvement by *Pneumocystis* of multiple extrapulmonary organs [32, 40].

Particularly in the critically ill patient, empirical therapy for PCP is warranted pending definitive diagnostic testing. Antimicrobial management options are outlined in Table 3. Primary antimicrobial agents include trimethoprim-sulfamethoxazole (TMP-SMX) and pentamidine isethionate. Both are equally effective [32, 41], but each has distinct advantages, disadvantages and toxicities. Changes in therapy necessitated by drug toxicity are not associated with adverse outcomes, whereas the need for a change in treatment because of clinical failure of one therapeutic agent is associated with lower survival rate [41].

TMP-SMX provides broad-spectrum coverage against a variety of Gram-positive and Gram-negative organisms in addition to PCP. Initially, TMP-SMX should be given intravenously in the critically ill patient, but it is well-absorbed orally, allowing step-down to enteral therapy. However, TMP-SMX is poorly tolerated in HIV-infected patients: adverse reactions are reported in 44–100%, with severe toxicity requiring discontinuation in up to 57% [32]. The most common adverse effects are fever, rash (which may progress to Stevens–Johnson syndrome),

TABLE 3. Antimicrobial therapy of common infections in AIDS patients

Infection	Drug of choice	Dose/Route	Usual duration	Alternative therapy
Protozoa				
Toxoplasmosis (*Toxoplasma gondii*)	Pyrimethamine[1]	200 mg loading dose, then 75–100 mg PO once daily	4–6 wks[2]	Pyrimethamine *plus* (clindamycin 600–900 mg IV q6h until marked clinical improvement, then 450 m PO q6h), *or* (clarithromycin) 1000 mg PO bid), *or* (azithromycin 1200 mg PO once daily)
	Plus Sulfadiazine *Maintenance therapy*:	1–1.5 gm PO q6h	4–6 wks	
	Pyrimethamine[1]	25–50 mg PO once daily	Indefinite	Pyrimethamine[1] *plus* clindamycin 300–450 mg PO qid (at least 1200 mg daily)
	plus Sulfadiazine	500–1000 mg PO qid	Indefinite	
Cryptosporidiosis (*Cryptosporidium parvum*)	No proven effective therapy			Reports of resolution with antiretroviral therapy induced immune reconstitution. Azithromycin 600 mg PO daily *plus* paromomycin 1 gm PO bid for 4 weeks, then paromomycin alone 1 gm bid for 8 weeks.
Microsporidiosis (*Encephalitozoon intestinalis, Enterocytozoon bieneusi*)	Albendazole	400 mg PO bid	3 wks	Efficacy of albendazole demonstrated for *E. intestinalis* Reports of resolution with antiretroviral therapy induced immune reconstitution.
Giardiasis (*Giaria lamblia*)	Metronidazole	250 mg PO tid	5 d	(Albendazole 400 mg PO daily for 5 days) *or* (furazolidone 100 mg qid for 7–10 days), *or* (Tinidazole 2 grams once [not marketed in North America])
Amebiasis (symptomatic) (*Entamoeba histolytica*)	Metronidazole[3]	750 mg PO/IV tid	10 d	(Tinidazole 1 gm bid for 3 days [800 mg tid for 5 days for liver abscess] [not marketed in North America]), *or* (dehydroemetine[4] 1–1.5 mg/kg/d IM [maximum 90 mg/d] for up to 5 d)

TABLE 3 (Continued)

Infection	Drug of choice	Dose/Route	Usual duration	Alternative therapy
	followed by Iodoquinol	650 mg PO tid	20 d	An alternate luminal agent (e.g., diloxanide furoate 500 mg tid × 10 d, or paromomycin 500 mg qid × 7 d)
Isosporiasis (*Isospora belli*)	Trimethroprim, (TMP); sulfamethoxazole (SMX)	TMP 160 mg, SMX 800 mg (1 DS tablet) PO/IV qid	10 d[5]	Pyrimethamine 50–75 mg PO daily plus folinic acid 5–10 mg PO daily × 4 weeks
	Maintenance therapy Trimethoprim; sulfamethoxazole	1 DS tablet 3 ×/wk	Indefinite	Pyrimethamine 25 mg PO daily *plus* folinic acid 5 mg PO daily
Pneumocystosis (*P. carinii*)	*Intravenous therapy* Trimethoprim-sulfamethoxazole (TMP-SMX)	Based on TMP component 15–20 mg/kg/d IV, divided q6h	21 d	(Clindamycin 600 mg IV q6h *plus* primaquine 15–30 mg [base] PO daily) *or* (Pentamidine 4 mg kg/day IV)
	Oral therapy Trimethoprim	200 mg PO qid (or 5 mg/kg tid)	21 d	(Trimethoprim-sulfamethoxazole 2 DS tablets tid or qid), *or* (clindamycin 450 mg PO tid plus primaquine 15 mg [base] PO daily) *or* (atovaquone 750 mg PO tid)
	plus			
	dapsone	100 mg PO daily	21 d	
Fungi				
Candidiasis				
Oropharyngeal	Fluconazole	100 mg PO daily	7–14 d[6]	Itraconazole 100–200 mg/d[7], or Ketoconazole 200 mg/d or Clotrimazole 10 mg troche [dissolve in mouth 5 times/day]
Esophageal	Fluconazole	400 mg loading dose then 200 mg, PO daily	3 wks[6]	Ketoconazole 200–400 mg daily PO, *or* Itraconazole 200 mg daily PO[7], *or* Amphotericin B 0.3–0.6 mg/kg IV daily for 7–14 d
Fluconazole-refractory mucosal candidiasis (oral, esophageal	Itraconazole oral solution[7]	100 mg, PO bid (swish and swallow)	2 wks[6]	Higher dose fluconazole (200–400 mg/day), or Amphotericin B oral suspension 100 mg qid (swallow and swallow), or Amphotericin B 0.3–0.6 mg/kg/day IV for 1–2 weeks

TABLE 3 (Continued)

Infection	Drug of choice	Dose/Route	Usual duration	Alternative therapy
Candidemia	Amphotericin B	0.5–1.0 mg/kg, Daily, IV	Until total dose 0.5–1.0 g (2–3 wks)	Lipid formulation of amphotericin B (e.g. liposomal amphotericin B 3–5 mg/kg/day)
	Or Fluconazole (*C. glabrata* less susceptible, *C. kruseii* resistant)	400–800 mg daily IV (PO after 7 days)	14 days after last positive blood culture	
Focal invasive or disseminated	Amphotericin B	0.5–1.0 mg/kg, Daily, IV	Until total dose ≥ 1–2 g and clinical resolution	Fluconazole 400–800 mg PO/IV *or* lipid formulation of Amphotericin B (e.g. liposomal amphotericin B, 3–5 mg/kg/day)[8]
	Plus/minus 5-Flucytosine[9]	25 mg/kg q6h, PO/IV		
Cryptococcal meningitis (*Cryptococcus neoformans*)	Amphotericin B	0.7 mg kg, Daily, IV	2–3 wks, and clinical response[10]	Lipid formulation of amphotericin B
	Plus/minus 5-Flucytosine	25 mg/kg q6h, PO/IV		
	Then Fluconazole	400 mg, Daily, PO/IV	8 wks	Itraconazole 200 mg bid PO
	Maintenance therapy: Fluconazole	200 mg Daily, PO	Indefinite	Itraconazole 200 mg bid[11]. *or* Amphotericin B 1 mg kg IV, once *or* twice weekly indefinitely
Histoplasmosis (*Histoplasma capsulatum*)	Amphotericin B[12]	0.5–1.0 mg/kg, Daily, IV	Until total dose 1–2 g	Itraconazole 200 mg bid PO (after loading dose of 300 mg bid for 3 days) for 12 weeks for mild to moderate disease
	Maintenance therapy: Itraconazole[7,13]	200 mg, Daily, PO	Indefinite	Fluconazole 400 mg/day (less effective) *or* Amphotericin B 1 mg/kg 1–2 times/week

TABLE 3 (Continued)

Infection	Drug of choice	Dose/Route	Usual duration	Alternative therapy
Coccidioidomycosis: (*Coccidioides immitis*)				
Extrameningeal	Fluconazole	400–800 mg PO/IV, daily	Indefinite	Itraconazole 200 mg bid *or* ketoconazole 400 mg bid[7] *or* amphotericin B 0.5–1.0 mg/kg/day IV until a total dose of 1.0–2.0 mg/kg
Meningitis	Fluconazole	400–800 mg, PO/IV daily	9–12 months	Amphotericin B 0.5–1.0 mg/kg/day IV until total dose 1–2 g IV*plus* intrathecal[14] amphotericin 0.1–0.3 mg 3 times per week long term, or itraconazole 200 mg bid[7], *or* ketoconazole 800–1200 mg/day[7]
	Maintenance therapy: Fluconazole	400 mg, PO daily	Indefinite	Itraconazole 200 mg bid, *or* ketoconazole 400 mg bid[7], *or* (if only extrameningeal disease, then Amphotericin B 1 mg/kg weekly)
Viruses				
Herpes simplex				
Mucocutaneous	Acyclovir	400 mg PO 3–5 times daily	10 d[15]	Famciclovir 500 mg PO bid (*or* 250 mg tid) for 5–10 days *or* valacyclovir 1 gm PO bid
Severe or refractory[16] mucocutaneous	Acyclovir	2.5–5 mg/kg, IV q8h (infused over 1 hr)	7–10 d[15]	Acyclovir 800 mg PO 5 times daily, *or* valacyclovir 1 gm PO bid, or famciclovir 500 mg PO bid or tid, *or* foscarnet 40–60 mg/kg IV q8h (infusion over 1 hr by infusion pump), or trifluridine (topically) in a 5% ophthalmic solution
Visceral or disseminated	Acyclovir	10 mg/kg, IV q8h (infusion over 1 hr)	10 d	Foscarnet 60 mg/kg IV q8h (infusion over 1 hr by infusion pump)
Herpes zoster				
Dermatomal	Famciclovir	500–750 mg, PO q8h	7 d	Acyclovir 800 mg PO 5 times daily or 10–12 mg/kg IV (infusion over 1 hr) q8h, *or* foscarnet 40 mg/kg IV q8h (infusion over 1 hr by infusion pump)
	Or			
	Valacyclovir	1000 mg PO tid	7 d	

TABLE 3 (Continued)

Infection	Drug of choice	Dose/Route	Usual duration	Alternative therapy
Disseminated (cutaneous or visceral) or ophthalmic	Acyclovir	10–12 mg/kg, IV q8h (infusion over 1 hr)	7–14 d	Foscarnet 40–60 mg/kg IV q8h (infusion over 1 hr by infusion pump)
CMV (cytomegalovirus)	Ganciclovir[17]	5 mg kg, IV q12h	14–21 d	Foscarnet 90–100 mg/kg IV q12h (infusion over 2 hr by pump); or cidofovir 5 mg/kg (protocol for probenecid + IV saline pre/post dose) weekly ×2 doses, then q2weeks; on intraocular ganciclovir implant + oral ganciclovir 1.5 gm tid
	Maintenance therapy[18]			
	Ganciclovir	5 mg/kg, IV daily	Indefinite	Ganciclovir 6 mg/kg IV daily (5 days/week); or foscarnet 90–120 mg IV (infusion over 2 hr by pump) once daily 5–7 days/week; or other options for CMV retinitis (ganciclovi 1–1.5 gm PO tid +/– intraocular ganciclovir implant; or cidofovir [as above])
Bacteria				
Streptococcus pneumoniae:				
Uncomplicated pneumonia	Penicillin G[19]	2 million units IV q4–6h	7–10 d	Cephalosporin (e.g. cefuroxime 0.75–1.5 g IV q8h, or ceftriaxone 1–2 gm IV q24h); *or* levofloxacin 500 mg PO/IV daily; or a macrolide (e.g. azithromycin 500 mg IV/PO daily, or erythromycin 500 mg IV q6h); *or* vancomycin
Pneumonia (decreased pneumococcus susceptibility)				
Intermediate resistance (penicillin MIC 0.12–1.2 ug/ml)	Ceftriaxone	2 gm IV daily	7–10 d	Cefotaxime; high dose penicillin G (>10 million units/days); or levofloxacin 500 mg IV/PO daily; or imipenem
High level resistance (penicillin MIC ≥2 ug/ml)	Vancomycin Or	15 mg/kg IV q12h	7–10 d	Imipenem 500 mg IV q6h; *or* cefotaxime or ceftriaxone (if cefotaxime and ceftriaxone MIC ≤2 ug/ml). For empiric

TABLE 3 (Continued)

Infection	Drug of choice	Dose/Route	Usual duration	Alternative therapy
	Levofloxacin	500 mg IV/PO daily	7–10 d	treatment of community-acquired meningitis: 3rd generation cephalosporin (cefotaxime 2 gm IV q4h or ceftriaxone 2 gm q12h) plus high dose vancomycin 15 mg/kg IV q6h
Staphylococcus aureus Pneumonia, bacteremia (uncomplicated)				
• methicillin susceptible (MSSA)	Nafcillin *or* oxacillin *or* cloxacillin[20]	2 g IV q4h	14 d	Vancomycin 15 mg kg IV q12h, or cefazolin 2 g IV q8h
• methicillin resistant (MRSA)	Vancomycin	15 mg/kg IV q12h	14 d	Teichoplanin (not available in North America) or Linezolid
Hemophilus influenzae pneumonia	Ceftriaxone	1–2 g IV q24h	10–14 d	Ampicillin 1–2 g IV q6h (if susceptible) *or* cefotaxime 1–2 g IV q6–8h *or* cefuroxime 0.75–1.5 g IV q8h or trimethoprim-sulfamethoxazole, or ciprofloxacin
Salmonella Bacteremia	Ciprofloxacin	750 mg, PO q12h	2–4 wks	Ampicillin 2 g IV q4–6h for 1–4 weeks (if susceptible), then amoxicillin 500 mg tid to complete a 2–4 week course or therapy[21], or cefotaxime *or* ceftriaxone, *or* trimethoprim-sulfamethoxazole
Listeria Meningitis	Ampicillin *plus*	200 mg/kg/d IV, divided q4h	3–6 wks	Trimethoprim-sulfamethoxazole 20 mg/kg/day (based on the trimethoprim component) divided q6h; or meropenem 1 g IV q8h
	Gentamicin[22]	2 mg/kg, IV q8h	2–6 wks	The risk/benefit considerations may favour stopping the gentamicin after 2–3 weeks there has been a good clinical response
Syphilis[23] Early (primary and secondary)	Benzathine penicillin G[24]	2.4 million units, once, IM		Doxycycline 100 mg PO bid for 4 weeks[25]

TABLE 3 (Continued)

Infection	Drug of choice	Dose/Route	Usual duration	Alternative therapy
Latent (>1 yr duration)				
• spinal fluid studies negative	Benzathine penicillin G[26]	2.4 million units, weekly, IM	3 wks (3 doses)	If no spinal fluid examination then consider one of follow regimens: Aqueous crystalline penicillin G 12–24 million units/day divided q4h IV for 10–14 days; *or* procaine penicillin G 2–4 million units IM *plus* probenecid 500 mg qid PO; or ceftriaxone 1 g IV/IM daily for 10–14 days[26,27]
Neurosyphilis	Aqueous crystalline penicillin G	18–24 million units IV q4h	10–14 d	Ceftrizxone 1 g IM or IV daily for 14 d *or* procaine penicillin G 2.4 million units IM daily *plus* probenecid 500 mg PO qid for 10 d[27,28]
Mycobacteria	Isoniazid[29]	300 mg, PO daily	9 mo[30]	An empiric regimen for suspected multidrug resistant TB (MDR–TB, ie resistant to INH and rifampin) may include: a parenteral drug (amikacin), plus a fluoroquinolone (ciprofloxacin or levofloxacin), plus ethambutol, plus pyrazinamide, plus INH, plus rifabutin, plus cycloserine (or ethionamide, or amino salicylic acid)
Mycobacterium tuberculosis	*plus* Pyridoxine (vitamin B6)	50 mg, PO daily	9 mo	
	plus Rifampin[31]	600 mg, PO/IV daily	9 mo	
	plus Pyrazinamide	20–30 mg/kg, PO daily	2 mo	
	plus/minus Ethambutol[32]	25 mg/kg, PO daily	2 mo	
M. avium complex (MAC)	Clarithromycin	500 mg, PO bid	Indefinite	Azithromycin 500 mg daily *plus* ethambutol 15 mg/kg/d is less effective[33]
	plus Ethambutol	15 mg/kg, PO daily	Indefinite	
	plus/minus Rifabutin	300 mg, 12 h, PO	Indefinite	

[1] Pyrimethamine should be used in conjunction with folinic acid (10–50 mg d for primary therapy, 10–20 mg d for maintenance therapy) in order to minimize hematologic toxicity (anemia, leukopenia, thrombocytopenia). AZT should be used with caution or withheld during the acute phase of treatment of toxoplasmosis.

[2] Primary therapy for toxoplasmosis should be continued until complete resolution or marked improvement has occurred clinically and radiologically (usually 4–6 weeks).

[3] Indicated for intestinal disease and or liver abscess. Asymptomatic cyst passers may be treated with a luminal agent, e.g., iodoquinol 650 mg tid for 20 d (alternative: diloxanide furoate 500 mg tid for 10 d or paromomycin 25–30 mg kg d divided in 3 daily doses for 7 d). Chloroquine phosphate 600 mg base (1 g)/d for 2 d, then 300 mg base (500 mg) d for 2–3 weeks may be used in the management of amebic liver abscess.

TABLE 3 (Notes to Table 3)

[4] Because of the potential for cardiotoxicity, patients receiving dehydroemetine should remain sedentary and have electrocardiographic monitoring.

[5] Continue treatment for 3 more weeks with trimethoprim (160 mg)-sulfamethoxazole (800 mg) 1 DS tablet PO, bid.

[6] Mucosal candidiasis in HIV patients has a high relapse rate. Intermittent or continuous maintenance therapy (systemic or topical) may be required.

[7] Take ketoconazole tablets or itraconazole capsules with food or cola. However, itraconazole solution is best absorbed fasting.

[8] Lipid formulations of amphotericin B are less nephrotoxic than conventional amphotericin B, but more expensive.

[9] Consider addition of 5-flucytosine in patients with overwhelming infection or local involvement with meningitis or endophthalmitis.

[10] Patients should receive amphotericin B with or without 5-flucytosine (100 mg/kg/day in 4 divided doses) until significantly improved and stable (usually by 2–3 weeks), at which time treatment can be changed to fluconazole 400 mg d PO/IV to complete a 10-week course of treatment. Itraconazole 200 mg bid PO is an alternative to fluconazole in this situation provided that drug interactions and poor absorption are not a concern.

[11] High relapse rate (24%) associated with lower dose of itraconazole 200 mg daily.

[12] Amphotericin B is indicated for disease which is moderate to severe or involves the central nervous system. Itraconazole effective for mild disease.

[13] Relapse rate is lowest with itraconazole, 5%; amphotericin B 19%, fluconazole 33%, and ketoconazole 50%.

[14] IT amphotericin B (cisternal, cervical, ventricular, or lumbar) should be started at a low dose (0.01–0.025 mg) and increased gradually as tolerated to a dose of 0.1–0.3 mg 3 times weekly. The best intrathecal route of administration is cisternal. IT amphotericin B should be given 3 times per week for 3 months then 1–2 times per week for several months. Further dosage tapering is based upon clinical course and spinal fluid parameters.

[15] Treatment should be continued until all lesions have crusted. Long-term suppressive therapy (acyclovir 200–400 mg 3–4 times daily) may be required to control frequent relapses.

[16] Foscarnet IV, high dose continuous IV acyclovir, topical trifluridine, or topical cidofovir may be used to treat acyclovir-resistant (thymidine-kinase-deficient) *Herpes simplex* infection.

[17] AZT should be discontinued during ganciclovir treatment in most cases because of additive hematologic toxicity (granulocytopenia). If long-term ganciclovir is indicated, then consider substituting alternate antiretroviral therapy or granulocyte colony stimulating factor to manage dose-limiting neutropenia (<500 cells/mm^3).

[18] Maintenance therapy is required for CMV retinitis but is controversial for gastrointestinal involvement.

[19] Patients receiving sulfa as PCP prophylaxis may develop pneumonia with sulfa-resistant bacterial pathogens.

[20] Vancomycin is the drug of choice for empiric therapy in areas where methicillin-resistant *S. aureus* is encountered, but is less effective than penicillinase-resistant synthetic penicillins against methicillin-susceptible *S. aureus* infections.

[21] If recurrence of bacteremia, then consider indefinite ciprofloxacin 500 mg bid or trimethoprim-sulfamethoxazole.

[22] Some authors also recommend intrathecal gentamicin.

[23] Some authorities advise CSF examination and or treatment with a regimen appropriate for neurosyphilis for all patients coinfected with syphilis and HIV, regardless of the clinical stage of syphilis. HIV-infected patients should have frequent follow-up and serologic testing at 1, 2, 3, 6, 9 and 12 months. Any patient without a 4-fold decline in nontreponemal serology by 3 months for primary or secondary syphilis, or 6 months in early latent syphilis, or a 4-fold rise in titer at any time should have a CSF examination and be treated with the neurosyphilis regimen unless reinfection can be established as the cause of the increased titer.

[24] Failed therapy and development of neurosyphilis has been reported with benzathine penicillin. CSF abnormalities are common in early syphilis in HIV patients and are of uncertain prognostic significance. Some authorities recommend CSF examination and modification of treatment accordingly.

[25] Treponema-cidal antibiotics (e.g. penicillin rather than doxycycline) are preferred for syphilis in HIV-infected patients. Document penicillin allergy (history +/− skin testing) and consider desensitization.

[46a] HIV-infected patients who have late syphilis should undergo cerebrospinal fluid examination. Those patients who have a normal spinal fluid examination (including negative CSF VDRL) do not require high-dose IV penicillin therapy and should receive benzathine penicillin G 2.4 m.u. IM weekly for 3 doses.

[26] Asymptomatic neurosyphilis is present in 1/2 of such patients. Therapy with either benzathine penicillin GIM or ceftriaxone IV/IM is associated with serologic or clinical failures in >20% of HIV-infected patients with latent syphilis or asymptomatic neurosyphilis.

[27] Since the durations of these regimens are shorter than that recommended for latent syphilis, some authorities recommend benzathine penicillin 2.4 million unit IM (once) after completion of any of the 10–14 day regimens (MMWR 1993; 42[RR–14]:36).

[28] Significant failure rate in HIV-related neurosyphilis, even with high dose IV penicillin.

[29] Isoniazid: higher dose of 10 mg/kg recommended for tuberculous meningitis until clinical response observed.

[30] Antituberculous therapy should be continued for 9 months or at least 6 months after conversion to culture negative state.

[31] Rifampin dose of 10 mg/kg if bodyweight below 50 kg.

[32] Ethambutol not required unless regional INH resistance is 4% or higher, or if drug resistance or disseminated disease is known or suspected.

[33] Neither amikacin nor clofazimine have been shown to improve outcomes in randomized clinical trials. Clofazimine has recently been associated with shorter survival in combination therapy.

leukopenia and other cytopenias, hepatic and renal dysfunction, hyponatremia and hyperkalemia, and gastrointestinal upset [20, 32]. However, many adverse effects can be managed successfully with supportive care, antihistamines, antipyretics and even corticosteriods, and desensitization to the drug can be carried out safely [20, 32]. TMP-SMX must be administered several times daily and intravenous doses require a large volume of fluid for dilution. PCP resistant to TMP-SMX is increasingly frequent, is likely to become more common and more clinically significant as the HIV pandemic grows and as TMP-SMX and the similar dihydropteroate synthase inhibitor, dapsone, are used more often for prophylaxis [35, 42]. A recent analysis identified resistance to sulfa drugs as a microbiologic factor associated with a poor outcome in patients with PCP. Mutations in the dihydropteroate synthase (DHPS) gene of *P. carinii* were found in 31 (20.4%) of 152 episodes of PCP. *P. carinii* DHPS mutations were independently associated with significantly lower short-term survival after diagnosis of PCP. Interestingly, the rate of DHPS mutations was closely related with the rate of previous or current use of sulfa drugs as chemoprophylaxis [43].

Pentamidine isethionate, in contrast, is only available parenterally (preferably used intravenously) and is administered once daily; the aerosolized form is appropriate for prophylaxis but not for the treatment of AIDS-related PCP, because of its association with extrapulmonary PCP [20, 32]. Of the various potential respiratory pathogens in AIDS patients, pentamidine has activity only against *Pneumocystis carinii*. Adverse effects are common, may be life-threatening and result in need to change therapy in up to 80% of patients [32]. Immediate reactions (many related to rate of infusion) include tachycardia, hypotension, flushing, syncope and hallucinations. Other reactions include fever, rash, gastrointestinal upset, cytopenias, hyponatremia and renal dysfunction. Hypoglycemia due to stimulation of insulin release may occur and prolonged pancreatic β-cell stimulation may progress to chronic glucose intolerance and even insulin-dependent diabetes. Prolongation of the QTc interval on electrocardiogram has been reported with evolution to polymorphic ventricular tachycardia (torsades de pointes). Magnesium depletion related to chronic malnutrition in the setting of advanced HIV disease may increase the likelihood of cardiotoxicity. Pancreatitis may occur and the risk of this complication may be worsened by the coadministration of pentamidine with antiretroviral agents (such as didanosine) which also are associated with pancreatitis [20]. Didanosine is contraindicated in patients receiving pentamidine.

Alternative anti-*Pneumocystis* agents include dapsone (particularly combined with trimethoprim), clindamycin-primaquine, atovaquone and trimetrexate [20, 32]. Clindamycin-primaquine and dapsone-trimethoprim have similar efficacy to TMP-SMX in patients with mild-to-moderate disease; dapsone-trimethoprim has been found to be better tolerated than TMP-SMX [32]. The spectrum of adverse effects of both drug combinations is similar to those of TMP-SMX, but dapsone and primaquine can produce methemoglobinemia (especially in patients with glucose-6-phosphate dehydrogenase deficiency), which may require discontinuation of the drug. While clindamycin can be administered both intravenously and enterally, the other agents are only available orally. Neither atovaquone nor trimetrexate has been shown to be effective enough to recommend use in the critically ill patient with PCP and both drugs are associated with significant adverse effects [20, 32].

Hence, TMP-SMX and pentamidine represent first-line agents for treatment of PCP. Presently, if tolerated, TMP-SMX remains the preferred first choice in the critically ill patient, because of its broader antibacterial spectrum (an advantage if the diagnosis is not clear or if more than one etiology is suspected). Prior use of sulfa medication as prophylaxis does not abrogate the choice of TMP-SMX as the preferred agent. However, if clinically significant sulfa resistance becomes more prevalent, this recommendation will

require reevaluation. If previous sensitivity to TMP-SMX is known or TMP-SMX is not tolerated, then pentamidine isethionate is favored. In that instance, if there is concern of an alternate etiology, such as bacterial infection, additional antibiotic treatment is warranted. If pentamidine is used, appropriate precautions and monitoring for adverse effects are necessary, although the drug can be used safely outside of an intensive care setting.

Corticosteroids were shown initially to be beneficial as an adjunct to anti-*Pneumocystis* drugs in therapy of PCP-related acute respiratory failure [44]. Adjunctive therapy with corticosteroids is recommended in moderate-to-severe PCP (initial PaO_2 on room air of <70 mmHg) [36], but benefit may be seen even in milder PCP [45]. Corticosteroids attenuate the inflammatory response to infection with *Pneumocystis*, which is exacerbated by microbial killing when anti-*Pneumocystis* agents are instituted [46]. The suggested dose is prednisone 40 mg orally twice daily for seven days, followed by 40 mg daily for seven days, and then 20 mg daily for seven days [36]. Initially, the equivalent dose of hydrocortisone is preferred in the critically ill patient. Adjunctive corticosteroid therapy should be started at the time antimicrobial agents are initiated and continued throughout the course of treatment to prevent early deterioration.

Response to PCP therapy may not be seen for five to seven days [32]. Corticosteroids ameliorate initial deterioration in the early treatment phase and there may be significant improvement in the first three days [43]. Thus, patients treated maximally with combined anti-*Pneumocystis* drugs and corticosteroids who fail to improve within three to five days should be evaluated thoroughly to rule out potential intercurrent infections, other complications (such as fluid overload or pneumothorax) or alternative diagnoses. Lack of improvement after seven days suggests resistance and warrants a trial of an alternative anti-*Pneumocystis* agent [20].

As a consequence of the severe compromise of lung compliance in patients who develop respiratory failure due to PCP, in the early years of the HIV epidemic, standard ventilatory strategies often resulted in application of very high mean airway pressures. In addition, infection with *P. carinii* also causes formation of bullae and lung cysts. These factors likely account for the high incidence of pneumothoraces reported previously [6]. Although mechanical ventilation using newer lung protection strategies may limit ventilator-induced lung injury and improve outcome [47], their use remains controversial [48, 49] and changes in outcome related to modality of mechanical ventilation for respiratory failure due to PCP have not been studied.

A recent trial of low (5 ml/kg) versus high tidal volume (12 ml/kg) in ARDS found significantly decreased mortality in the low (approximately 30%) versus the high tidal volume (approximately 40%) [50]. Therefore, we suggest ventilation using lung protective low tidal volume because of the similarities of PCP and ARDS. Continuous positive airway pressure delivered by face mask has been shown to be efficacious for relief of hypoxia and reduces work of breathing among patients with respiratory failure related to PCP, but it is not clear that such treatment affects patient outcome. Patients who fail such support and require intubation have a high mortality rate [51].

Acute respiratory failure (ARF) related to PCP has a very poor prognosis, which thus raises questions regarding the appropriateness of offering critical care support to such patients. However, the outcome of PCP-related ARF has varied through the AIDS epidemic, largely due to changes in patient selection for ICU support and because of increased use of corticosteroids as adjuvant therapy [6]. Thus, investigators have attempted to identify subgroups destined to have a high mortality in order to advise patients about treatment options. Consequently, many tools have been developed to identify predictors of outcome of PCP-related ARF in AIDS [6]. Based on this work, it seems the degree of physiologic dysfunction in multiple organ systems on

presentation to ICU is an important determinant of outcome in acute respiratory failure due to AIDS-related PCP [52]. This supports previous findings of the predictability of physiological scores in other critically ill populations [6].

In addition, it has been demonstrated that mortality amongst patients who develop ARF after at least five days of maximal therapy with anti-PCP drugs and corticosteroids is higher than that of patients with fewer than five days of prior maximal therapy [39, 53]. The importance of duration of maximal therapy as a predictor of in-hospital mortality may be related to the pathophysiology of pneumocystosis. Since initiation of anti-PCP therapy may exacerbate the inflammatory response by antimicrobial killing of *Pneumocystis* organisms [36] resulting in deterioration of oxygenation during the first three to five days of treatment [44], such a deterioration in gas exchange may precipitate respiratory failure. Even adjunctive corticosteroids within the first five days of therapy may not be sufficient to prevent early development of respiratory failure. Nevertheless, since acute respiratory failure in the early stages of therapy is due to an acute inflammatory process, it may be reversible. In contrast, development of respiratory failure despite five or more days of maximal therapy may represent the consequence of progression of pulmonary parenchymal inflammation to early fibrosis with poor prognosis.

The long term prognosis of PCP survivors also affects decision making about critical care support for patients with PCP and acute respiratory failure, since anticipated longevity may also influence the value patients place on critical care support. However, while some studies have documented a worse long-term prognosis for patients requiring admission to ICU than for patients who do not develop respiratory failure, others have not found this and excellent potential long-term survival has been emphasized [6]. This is especially relevant in the modern era of antiretroviral therapy. A recent study found that in-hospital survival was lower for patients with PCP who develop acute respiratory failure, but their long-term survival was no different from that of patients with PCP who do not develop respiratory failure [39] (Figure 5).

TUBERCULOSIS AND OTHER MYCOBACTERIAL INFECTIONS

Although tuberculosis itself remains a devastating infectious illness in the developing world, the disease is a major problem in the HIV-infected population globally. It is estimated that about 40% of HIV-seropositive persons worldwide and more than 8% of HIV-infected individuals in North America are co-infected with *Mycobacterium tuberculosis* [54, 55]. In the United States, there are thought to be 6000–9000 new tuberculosis infections annually in HIV-positive persons [54, 55] and at least 21% of persons with tuberculosis are also infected with HIV [56]. In the developed world, tuberculosis is especially common in indigent persons and among those who use illicit drugs, one-third of whom also are infected with HIV [55].

HIV-positive individuals are at high risk of developing tuberculosis through primary or exogenous recurrent infection or reactivation of latent disease. This susceptibility is related to T-lymphocyte cytokine responses, which are altered in the setting of HIV infection [55]. Alteration of cell-mediated immunity by HIV infection therefore reduces host ability to contain latent infection and to resist reinfection and contributes to the rapid progression of clinical disease [56]. Further, co-infection with *Mycobacterium tuberculosis* and HIV seems to have detrimental effects on the natural course of HIV infection. For example, *M. tuberculosis* seems to upregulate HIV replication in alveolar macrophages and lymphocytes, possibly by induction of cytokines with resultant cellular stimulation. Clinical studies have also shown that the mortality rate of HIV-infected individuals with tuberculosis is doubled and seems due to more rapid progression of HIV disease rather than tuberculosis [55]. Hence, all patients with tuberculosis should be tested for HIV infection [55].

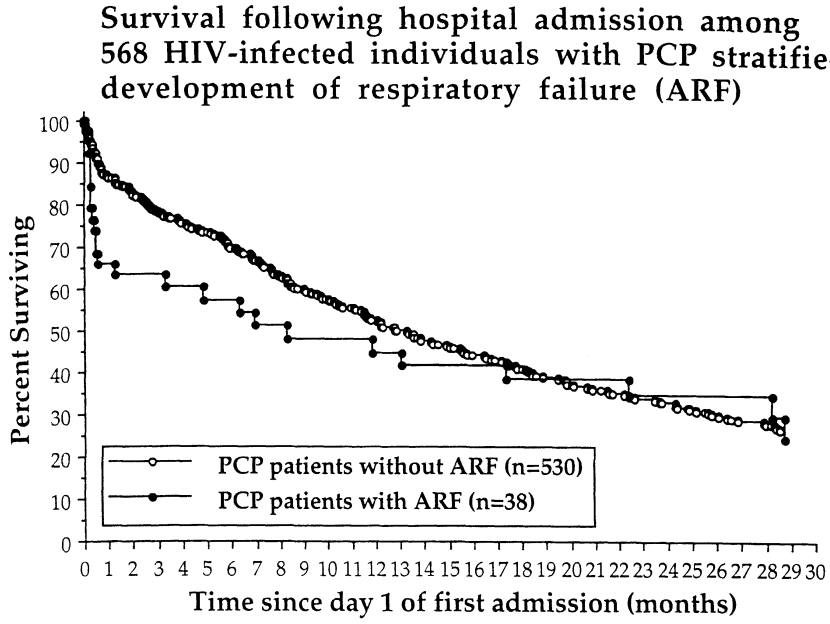


FIGURE 5. Long term survival from date of first hospital admission of patients with AIDS-related PCP and acute respiratory failure (ARF) compared with AIDS patients with PCP who did not develop respiratory failure at St. Paul's Hospital between 1991 and 1996. There is no difference in the survival curves between the two patient groups ($p = 0.798$). PCP patients with ARF ($n = 38$) - closed circles. PCP patients without ARF ($n = 530$) - open circles. (Reproduced with permission from Forrest *et al.* (39).)

Clinical manifestations of tuberculosis in the setting of HIV infection are protean, depending on the level of immunosuppression [55]. Constitutional symptoms characteristic of tuberculosis are nonspecific and similar symptoms are common with HIV infection itself [20]. The presentation of tuberculosis is more typical early in the course of HIV infection, while mycobacteremia and extrapulmonary disease are more common at later stages of immunosuppression [55, 56]. Reactivation tuberculosis in the HIV-infected person may have radiographic features of primary tuberculosis, including intrathoracic lymphadenopathy, mid- and lower-zone infiltrates, pleural effusions and miliary pattern [20]. Upper-zone infiltrates and cavitation found with tuberculosis in the non-HIV-infected individual are more frequent in persons with CD4+ count more than 200 cells/μl [55]. Approximately 5% of patients have a normal chest radiograph with positive sputum smears [20, 55].

Although prospective tuberculin skin testing has been shown to be useful in HIV-infected individuals, it has no clinical utility as a diagnostic test when active tuberculosis is considered, for several reasons [20]. First, the tuberculin skin test is often minimally or not reactive in advanced HIV disease because of suppression of cell-mediated immunity. While skin test reactivity may be preserved early in the course of HIV infection, the prevalence of anergy increases as the CD4+ count declines [56]. Second, active tuberculosis can result in specific anergy to mycobacterial antigens, even in HIV-negative patients, so that the tuberculin skin test may be nonreactive.

Diagnosis of tuberculosis should be based on the identification of the organism on smear and culture of clinically infected tissue or lower

respiratory tract secretions [20]. Recently, a number of rapid diagnostic tests have been developed. Using polymerase chain reaction (PCR), ribosomal RNA or DNA of *M. tuberculosis* can be identified in clinical specimens (e.g., sputum) within 24 hours [55]. The tests are used in smear-positive cases in patients who have received fewer than seven days of anti-tuberculous therapy, where sensitivity and specificity of the tests are greater than 95%. However, the availability of these tests does not obviate the need for acid-fast staining of lower respiratory secretions, which is necessary to gauge contagiousness. PCR tests are not indicated for HIV-infected patients with positive acid-fast smears in whom clinical suspicion of tuberculosis is high, since a negative test does not rule out tuberculosis. Similarly, if clinical suspicion of tuberculosis is high and acid-fast smears are negative, anti-tuberculous therapy is indicated regardless of the results of the rapid diagnostic tests. If smears are negative and suspicion of tuberculosis is low, clinical decision making will not be altered by the result of a rapid diagnostic test, since a positive result is likely to be a false positive in this context [55]. Finally, analysis of *M. tuberculosis* by restriction-fragment-length polymorphisms can allow identification of specific strains of *M. tuberculosis*, which can be useful in epidemiologic analysis and identification of multidrug resistant strains [55].

Recommended therapy for tuberculosis in the HIV-infected host is outlined in Table 3. Therapy should be continued for a minimum of six months. Several studies have documented improved effectiveness with more prolonged antituberculous therapy (9–12 months) in the setting of HIV infection [54, 55]. There have been reports of malabsorption of anti-tuberculous medications in HIV-infected patients, but pharmacokinetic studies have produced conflicting results and measurement of plasma drug levels is unwarranted [55].

Explosive outbreaks of multidrug resistant tuberculosis were associated with mortality rates as high as 89% in HIV-infected persons [55, 56]. However, use of two or more effective anti-tuberculous drugs has increased survival among HIV-positive patients. Most deaths among patients treated effectively are due to complications of HIV infection rather than due to tuberculosis [54–56]. Isolated resistance to isoniazid is the most common form of reduced susceptibility, but alternative therapy is associated with a good outcome. Rifampin resistance is uncommon, but when present, it is usually found in the setting of HIV infection; therapy with alternative regimens may need to be prolonged [54]. Multidrug resistance should be suspected in patients with persistent fever or lack of clinical response after 14 days of anti-tuberculous therapy [20].

The treatment of tuberculosis in HIV-positive persons has been affected by the advent of highly active antiretroviral therapy, for a number of reasons. First, there is substantial risk of drug interactions between anti-tuberculous medications and antiretroviral drugs, notably reduction in drug levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors by rifampin and (to a lesser extent) by rifabutin. Rifabutin seems to be of similar efficacy to rifampin and should be substituted for it if protease inhibitors are to be continued; the dose of the protease inhibitors may need to be increased to prevent emergence of drug-resistant HIV [54, 55]. Consultation with a specialist and/or pharmacist familiar with the treatment of HIV is advised. The second important HIV/tuberculosis interaction is that initiation of antiretroviral therapy shortly after starting treatment of tuberculosis has been associated with worsening of tuberculous disease in up to 36% of patients. Other causes of deterioration should be considered. Such paradoxical reactions are generally self-limited and resolve within 10 to 40 days, but may require a short course of corticosteroids [55].

Standard treatment of drug-susceptible tuberculosis in an HIV-positive patient results in sterilization of sputum and rates of failure similar to non-HIV-infected persons. However, more prolonged therapy may be necessary to prevent

relapse [55, 56]. Predictors of poor survival include low CD4+ count, absence of directly observed therapy, multidrug resistant *M. tuberculosis*, and history of injection drug use [54].

Nontuberculous mycobacterial infections have become more common in the setting of HIV infection largely as a consequence of improvements in the care of HIV-infected patients, particularly the advent of prophylaxis for other opportunistic infections and the use of antiretroviral drugs [56]. Over 95% of these infections are due to *Mycobacterium avium* complex (MAC) and usually represent disseminated disease. Significant MAC-related disease generally only occurs in the context of severe immunosuppression (CD4+ count fewer than 50 cells/μl). The recovery of MAC from the respiratory tract is usually not clinically relevant in the HIV-infected patient, unless associated with an endobronchial lesion or localized pulmonary disease in a susceptible host. On the other hand, the isolation of MAC from the respiratory tract in the absence of a localized process is usually associated with eventual disseminated disease and therefore is a marker of advanced HIV-induced immunosuppression [56]. The treatment of MAC infection is outlined in Table 3. Given the occurrence of MAC infection at a late stage of HIV disease and its disseminated nature, it is a rare cause or complication of ICU admission in the HIV-positive individual.

Other mycobacteria account for fewer than 5% of nontuberculous mycobacterial infections. *M. kansasii* can cause infection in patients with CD4+ count less than 200 cells/μl and usually produces pulmonary disease, although one quarter of patients have extrapulmonary involvement. Chest radiographs may show focal upper lobe infiltrates, diffuse interstitial disease or cavitation [56]. In general, isolation of *M. kansasii* from the respiratory tract of an HIV-positive patient warrants treatment. *Mycobacterium genavense* is a rare fastidious species that has been associated with disseminated disease in the HIV-infected patient, while *M. xenopi*, *M. haemophilum* and other miscellaneous nontuberculous mycobacteria can cause pulmonary and/or disseminated disease. Therapy for these infections is reviewed elsewhere [56], but generally they do not respond to standard anti-tuberculous medications and consultation with an Infectious Diseases specialist is recommended.

BACTERIAL PNEUMONIA

Bacterial infections, especially lower respiratory tract infections, occur more frequently than opportunistic infections in HIV-infected individuals and bacterial pneumonia is more common than PCP in the setting of HIV infection [57]. Indeed, more than one third of HIV-positive persons develop a serious bacterial infection during the course of their illness. The case definition of AIDS has been revised such that the occurrence of two or more episodes of bacterial pneumonia within a one-year period is diagnostic of AIDS. Nevertheless, bacterial infection in the HIV-positive patient often presents long before disease due to opportunistic pathogens [57].

Susceptibility to bacterial infection is related to the general immune dysfunction typical even in early HIV disease, although bacterial pneumonia becomes increasingly common as CD4+ count declines [57]. While the exact mechanism is unclear, HIV has deleterious effects on B-lymphocyte performance and hence antibody-mediated immune function. As a consequence, HIV-positive patients are predisposed to infection with encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Similar defects in monocyte-macrophage and neutrophil function with abnormal chemotaxis, phagocytosis and intracellular killing predispose to infection with organisms such as *Staphylococcus aureus*. In addition, neutropenia secondary to HIV-related medications (e.g. zidovudine, TMP-SMX, ganciclovir) can also increase the risk of bacterial infection. Finally, local pulmonary defense mechanisms, including alveolar macrophage, complement and surfactant function, are impaired in the setting of HIV infection [57].

The etiologies of bacterial pneumonia in the setting of HIV infection are similar to the causes of community acquired pneumonia in the non-HIV-infected population [57]. In particular, infection with *S. pneumoniae* and *H. influenzae* are common. Bacteremia is more common than in HIV-negative individuals. Previously thought to be a frequent pathogen causing pneumonia in the HIV-seropositive patient, infection with *Legionella* species is rare. On the other hand, while infection with Group B *Streptococcus* (*S. agalactiae*) is unusual in HIV-negative persons, it is more common in those with HIV disease. The incidence of *Staphylococus aureus* as a community acquired pathogen is increasing in HIV-infected injection drug users. The defective cell-mediated immunity characteristic of HIV infection predisposes HIV-positive persons to infection with *Nocardia*, which may cause abscess formation and pulmonary disease indistinguishable from tuberculosis. *Rhodococcus equi* is a Gram-positive bacillus which causes infection in immunocompromised hosts exposed to animals, especially horses. Such infection has been recognized more frequently in HIV-infected persons with a clinical presentation similar to nocardiosis or tuberculosis.

Hospitalized patients may develop nosocomial pneumonia [57]. This occurs most commonly in patients with advanced HIV disease, since these patients are most likely to require care in hospital. Additional predisposing factors include the presence of a central venous catheter and neutropenia. Gram-negative pathogens are the most frequent etiologies. Of note, *Pseudomonas aeruginosa* has been recognized as a more frequent pathogen in community acquired pneumonia in HIV-infected individuals.

The clinical features of bacterial pneumonia in HIV-seropositive persons are similar to those in non-HIV-infected patients [57]. Notably, bacterial pneumonia has a more fulminant presentation than the indolent course characteristic of PCP. While two-thirds of patients with bacterial pneumonia have lobar consolidation, up to 40% can have diffuse disease. Other features typical of bacterial pneumonia which are less frequent with other causes of respiratory disease in the HIV-positive patient include elevation of the white blood cell count with left shift, normal or only mildly elevated LDH levels, and CD4+ count greater than 200 cells/μl.

While recovery of the pathogen from lower respiratory tract secretions is essential, mere isolation of a pathogen does not necessarily signify infection, since colonization of the respiratory tract is common in chronically ill individuals [57]. Hence, a Gram's stain of expectorated sputum showing fewer than 10 epithelial cells and more than 25 white blood cells per high power field with organisms morphologically resembling those cultured subsequently is required to support a particular microbiologic diagnosis. Since bacteremic pneumonia can occur in the absence of positive samples of lower respiratory tract secretions, blood cultures should always be obtained. As noted previously, specimens obtained bronchoscopically are recommended, especially in critically ill patients, both to increase the yield for bacterial pathogens and to rule out co-infection of the lower respiratory tract (for example, with *Pneumocystis*) [20].

Treatment of bacterial pneumonia in the setting of HIV infection is outlined in Table 3. In general, therapy is the same as that for similar infection in immunocompetent hosts. Where PCP is suspected, trimethaprim-sulfamethoxazole provides coverage against many of the bacterial pathogens causing lower respiratory tract infection in the HIV-positive patient. However, since the combination is only bacteriostatic, if bacterial pneumonia is suspected strongly, especially in a critically ill patient, we recommend therapy including agents with bactericidal action, such as cefuroxime or ceftriaxone. Of note, pneumonia due to pneumococcus with intermediate sensitivity to penicillin (minimum inhibitory concentration of 1–4 μg/ml) can be treated adequately with penicillin G. If there is a high prevalence of penicillin-resistant pneumococci (minimum inhibitory concentration of

≥4 μg/ml), initial therapy with ceftriaxone or vancomycin is suggested with modification based on the results of microbiologic testing. Similarly, if *S. aureus* is suspected as the causative pathogen (based on the results of Gram's stain and/or culture) and there is a high prevalence of methicillin resistance, initial empiric therapy with vancomycin is recommended for the critically ill patient.

In general, the mortality due to bacterial pneumonia in the setting of HIV infection is similar to that in HIV-negative persons [58]. Although recurrences are more common, the outcome of pneumococcal pneumonia in HIV-infected individuals may be better than in HIV-seronegative persons [57]. On the other hand, the mortality rate of HIV-positive patients with Gram-negative nosocomial infection is higher [20]. Because of the high incidence of pneumococcal infection in HIV-positive persons, it is recommended they receive pneumococcal vaccine, although vaccine efficacy is less predictable than in HIV-seronegative individuals [57]. When possible, pneumococcal vaccine should be given when the CD4 cell count is greater than 200 cells/μl.

FUNGAL PNEUMONIA

Fungal infections are the most common opportunistic infections in HIV disease [59], but comprise fewer than two pulmonary infectious episodes per 100 person-years [60]. Fungal pneumonia tends to be a complication of late-stage HIV disease [20]. Resistance of fungi to nonimmune killing by polymorphonuclear leukocytes discriminates pathogenic from opportunistic fungi [61]. The former include *Cryptococcus neoformans* and agents of endemic mycoses which cannot be killed effectively by nonimmune phagocytes, so that an intact cellular immune system is necessary for effective host resistance to infection. Such infections occur in normal hosts, often with recovery. In contrast, spores of opportunistic fungi (such as *Aspergillus*) are killed by nonimmune phagocytes, so that infection characteristically occurs in patients with reduced neutrophil number or function; cell-mediated immunity is of little importance to host resistance to these fungi. Finally, *Candida* has features of both types of fungi: mucocutaneous candidiasis is more common with T-cell deficiency, while invasive candidal disease requires neutrophil dysfunction [62].

These divisions are somewhat artificial in the setting of HIV disease, as HIV-infected patients are actually more prone to developing infection by the "pathogenic" group of fungi, which are perhaps better described as T-cell opportunists in this setting. However, since neutrophil function is abnormal in HIV disease (especially late in disease and with concomitant depression of neutrophil number due to HIV-related medication, etc.), such patients are predisposed also to infection with fungi traditionally felt to be opportunists in the setting of phagocyte dysfunction. It is also noteworthy that the burden of fungal infection in patients with AIDS is generally higher than in those without HIV disease and is often systemic, making treatment more difficult [62].

Cryptococcosis is the most common fungal infection complicating AIDS [62]. *Cryptococcus neoformans* is an encapsulated fungus that is found worldwide, particularly in bird droppings, decaying fruit and soil. The organism enters the body by inhalation of spores with initial infection in the lung, although this is usually asymptomatic. However, pulmonary infection can occur with primary infection and the clinical and radiographic features resemble pneumocystosis. Onset is subacute with fever, cough and dyspnea in patients with pulmonary disease; on chest radiograph, diffuse interstitial infiltrates are typical, but radiographic manifestations can be protean. *Cryptococcus* has a remarkable trophism for the central nervous system, so patients with pulmonary disease should be presumed to have concomitant meningitis and systemic infection. Blood cultures for fungi, a serum cryptococcal antigen assay and a lumbar puncture should be performed. The serum cryptococcal antigen has high sensitivity and specificity: the test is posi-

tive in more than 98% of cases of cryptococcal meningitis. The organisms may be found on direct smear and culture of BAL specimens from the lower respiratory tract. While cryptococcal antigen can be found in lavage fluid, serum cryptococcal antigen is almost always positive and a negative cryptococcal antigen in lavage fluid does not rule out the disease. Currently recommended therapy is outlined in Table 3.

In highly endemic areas, infection with *Histoplasma capsulatum* exceeds cryptococcosis as an opportunistic fungal infection in patients with AIDS [62]. The organism is endemic to the major river valleys in North, Central and South America and the Caribbean [63], particularly in soil enriched by bird or bat droppings [62]. The organism is acquired by inhalation. Progression of primary infection is the most common mechanism of pulmonary disease in immunocompromised hosts, but pulmonary disease can also occur as a result of reactivation of previous infection [62]. The onset of illness is often subacute with nonspecific symptoms. The chest radiograph may be normal or may show a diffuse or miliary pattern, but localized infiltrates can also be seen [63]. Disseminated disease with diffuse involvement of the reticuloendothelial system and hepatosplenomegaly is common. Serum histoplasma polysaccharide antigen testing is highly sensitive, but cross-reaction can occur with paracoccidioidomycosis, blastomycosis and *Penicillium* infection. The organism can also be recovered by BAL on direct smear and culture. Treatment is amphotericin B for life-threatening or CNS histoplasmosis. Maintenance therapy with itraconazole is required for life. Itraconazole is the treatment of choice for mild to moderately severe disseminated histoplasmosis.

Coccidioidomycosis is endemic to arid and semi-arid climates in the southwestern United States, Central and South America. For most AIDS patients, disease is the result of new infection, acquired by the pulmonary route. The illness is principally respiratory but can be disseminated. Diagnosis can be established by recovery of the organism on BAL. Patients with advanced HIV disease have severe and often fatal illness. Initial treatment is with fluconazole or amphotericin B followed by lifetime maintenance therapy [62]. *Blastomyces dermatitidis* is co-endemic with *Histoplasma* over much of North America, but cases have also been reported in Africa, Central and South America, India and the Middle East. Infection in HIV seropositive individuals is rare and associated with aggressive pulmonary infection and rapid dissemination. The organism can be identified on BAL specimens. The infection has been incurable in AIDS patients [62]. *Paracoccidioidoes brasiliensis* is endemic to Central and South America. Paracoccidioidomycosis is also a rare complication of AIDS and produces aggressive pulmonary infection and widespread dissemination. The organism can be recovered on BAL. Prognosis in HIV positive patients is better, however, and the disease should be treated with amphotericin B and lifetime maintenance therapy with itraconazole [60].

Pulmonary aspergillosis was reported as a more common fungal infection in HIV patients than cryptococcal disease in one series [60] and is said to occur in 0.1–0.5% of patients [62]. The fungus is found worldwide in decaying organic matter. Infection is by the respiratory route and pulmonary disease is usual with primary infection. Intact phagocyte function is necessary for immunity and more than half of AIDS patients with aspergillosis have neutropenia, while most others have advanced HIV disease with CD4+ counts less than 50 cells/μl and severe phagocyte immune dysfunction. While presenting features are usually nonspecific, patients with cavitary and endobronchial lesions may have hemoptysis, which is rare in other pulmonary opportunistic infections [62]. Two distinct forms of pulmonary disease are seen: invasive parenchymal infection with localized or diffuse consolidation or cavitation, especially in the upper lobes, and bronchial disease with endobronchial lesions and even bronchial obstruction [62, 63]. Dissemination is common [63]. Diagnosis is best established

by bronchoscopy and biopsy of endobronchial lesions, if identified [62]. The mere recovery of the organism on BAL, however, does not distinguish colonization from invasive disease, although positive cultures of sputum or BAL specimens in the absence of an alternate etiology raise the likelihood of invasive disease. A definitive diagnosis can only be established by histopathologic evidence of tissue invasion on appropriate biopsy specimens; obtaining such biopsies may not be feasible in a critically ill patient. Treatment is outlined in Table 3. The prognosis for recovery in AIDS patients is poor [62], although occasional case reports suggest that survival time may be improved with highly active antiretroviral therapy.

Candidal infection of mucocutaneous sites is common and virtually all HIV-infected patients have mucosal candidiasis at some point during the course of their illness [62]. Infection with *Candida* can involve the trachea and upper bronchi but parenchymal disease is extremely uncommon. Mucocutaneous candidiasis can be treated with fluconazole [62]. Fluconazole-resistant mucosal candidiasis is associated with prolonged exposure to azoles and CD4+ lymphopenia. Management options include itraconazole oral solution and amphotericin B (oral solution or intravenous). Other fungal infections are rare in HIV-positive patients.

VIRAL INFECTIONS

The clinical effect of viral pulmonary infections in HIV disease is poorly defined. HIV itself can cause pulmonary disease and a lymphocytic alveolitis, but such disease is generally mild. It may contribute, however, to the development of lymphoid interstitial pneumonitis or nonspecific pneumonitis [64]. Primary influenza pneumonitis occurs with no greater frequency or severity in the setting of HIV infection than in non-HIV-infected individuals [64]. Treatment with amantadine, rimantadine or zanamivir must be started within 48 hours of symptom onset and is usually not effective. Ribavirin may be used for critically ill patients but is unproven. Infection of the lower respiratory tract with respiratory syncytial virus and rubeola (measles) virus is more common in HIV-infected children than in those without HIV disease. These viruses rarely produce severe pneumonitis in adults. Aerosolized ribavirin can be effective [64]. Adenovirus is an infrequent cause of pulmonary disease in HIV-positive patients, but can cause a fulminant and fatal disease for which there is no available treatment [64].

Infection of the lower respiratory tract with herpes simplex virus (both types 1 and 2) has been observed in 0.2–4% of autopsy series. Varicella-zoster virus (VZV) infection can occur occasionally in adults, but is more common in children. Diagnosis is difficult in the case of herpes simplex virus, since mere recovery of the organism from lower respiratory tract secretions does not signify infection. Instead, identification of histopathologic change (Cowdry type A intranuclear inclusions) in tissue specimens is necessary. Development of diffuse alveolointerstitial infiltrates in a patient with vesicular rash typical of primary VZV infection warrants treatment even in the absence of demonstrable histopathology of pulmonary specimens. Varicella-zoster pneumonitis has not been reported with cutaneous reactivation of infection (shingles) in AIDS patients. Both herpes simplex and VZV infections can be treated effectively with acyclovir. Ganciclovir also has activity against herpes simplex virus [64].

Cytomegalovirus (CMV) is the most frequently isolated virus from the respiratory tract in HIV-infected patients and active infection is found in up to 90% of cases of advanced HIV disease in autopsy series [64]. Its pathogenic importance, however, remains controversial [20]. CMV is seldom implicated clinically as a cause of pneumonitis, even though foci of CMV and inclusion bodies can often be found at autopsy [65]. The course of CMV pneumonitis in the setting of HIV infection certainly is not as fulminant as in the bone marrow transplant population, and it is likely that in most patients with AIDS, infection with CMV produces subclinical disease [64].

Even with the advent of corticosteroid use as adjunctive therapy for PCP, there has not been a rise in the incidence of clinical CMV pneumonitis [20]. The presence of CMV in patients with PCP does not seem to affect short- or long-term survival or length of hospital stay [65].

Seropositivity for CMV in the general population increases with age and homosexual men have a particularly high seroprevalence [64, 65]. Disease is due to reactivation of latent infection, can involve multiple organs and typically occurs at a late stage of HIV disease, when the CD4+ count is less than 50 cells/μl [20]. CMV pneumonitis in the context of AIDS should be diagnosed only if hypoxemia and diffuse pulmonary infiltrates coexist with the presence of CMV cytopathic effect (intranuclear and intracytoplasmic inclusions) in lung tissue without evidence of alternate etiologies [20, 65]. Treatment is suggested only if there is histologic evidence of infection and lack of response to treatment for other pathogens [65]. This is an important consideration in the critically ill, since therapy against CMV is associated with significant side effects (such as neutropenia with ganciclovir and renal dysfunction with foscarnet). Treatment is outlined in Table 3.

MISCELLANEOUS CAUSES OF CRITICAL PULMONARY DISEASE

A variety of other disorders can lead to respiratory failure in the HIV-positive patient. Reactivation of latent infection with *Toxoplasma gondii* is an infrequent cause of pneumonitis [64], though reported in 2% of patients with respiratory failure admitted to ICU in one study [21]. Pulmonary disease may occur as an isolated process or may coexist with disseminated or central nervous system disease. Diffuse bilateral infiltrates are typical, but a coarse nodular pattern may also be seen. The organism can be recovered on BAL [64]. Treatment is outlined in Table 3. Bronchopulmonary cryptosporidiosis has also been reported, although its significance as an isolated cause of pulmonary infection is unclear [64]. Pulmonary strongyloidiasis has occurred in patients with disseminated disease characteristic of autoinfection and is associated with a high mortality rate [64].

Kaposi's sarcoma (KS) is the most common malignancy in HIV-infected persons [63] and has been linked to infection with herpes virus type 8. Mucocutaneous disease is most common, but pulmonary involvement occurs in up to 25% of patients. Pulmonary disease in the absence of mucocutaneous lesions is rare [20]. Pulmonary KS is often indistinguishable from other HIV-related pulmonary disease. Hemoptysis and lymphadenopathy are frequent, pleural effusions are common, and endotracheal or endobronchial lesions can cause airway obstruction. Bronchoscopic visualization of the typical red-violaceous lesions is usually sufficient for diagnosis; BAL can rule out superimposed infection [20, 63]. Parenchymal disease can be difficult to diagnose, since transbronchial and even open lung biopsy are often unhelpful [63]. Chemotherapy with liposomal anthracyclines and paclitaxel can be effective [66], but respiratory failure related to KS has a poor prognosis [20].

Other malignant causes of pulmonary infiltration and disease include non-Hodgkin's lymphoma and solid tumors, including primary lung cancer. Lymphocytic interstitial pneumonitis, nonspecific interstitial pneumonitis, bronchiolitis obliterans and organizing pneumonia, and pulmonary hypertension may also cause respratory failure in HIV-seropositive patients [63]. Pleural effusions are usually parapneumonic or empyemas (including tuberculous) or are related to Kaposi's sarcoma; 20% may be transudates associated with hypoalbuminemia. Pneumothorax is most commonly encountered with PCP [38].

Neurologic Disease

Neurologic disease is the second most common cause for admission to the ICU among HIV-seropositive persons. Most of the cases in one series had space occupying lesions and fewer than 20% had meningitis [21]. Neurologic disease may also be a concomitant problem in patients

requiring ICU care for other reasons [20]. Involvement of the nervous system can be considered in terms of site of neuroanatomic localization of clinical dysfunction: meningitis, focal or diffuse central nervous system (CNS) disease and peripheral nervous system disease (myelopathy and peripheral neuropathy), and ocular disease. The assessment of neurologic complications in HIV-positive patient is based on three tenets: neuroanatomic localization of dysfunction, temporal profile of its evolution, and consideration of the stage of HIV infection [67]. Both meningitis and parenchymal CNS disease can present with headache and/or CNS dysfunction; an approach to the management of such patients is outlined in Figure 6.

MENINGITIS AND MENINGOENCEPHALITIS

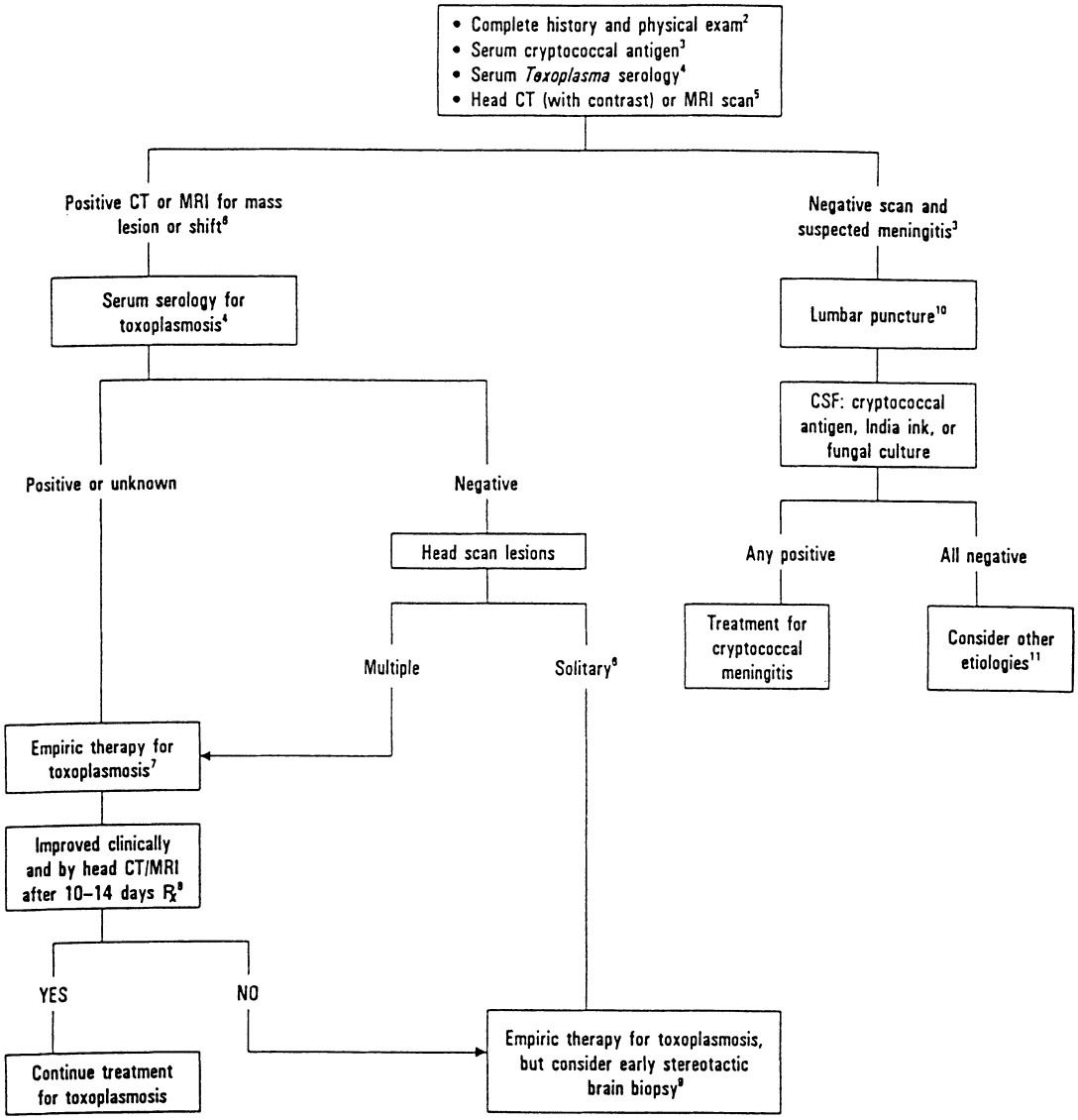
The clinical presentation of meningitis in the HIV-positive patient may be different from that typical of an immunocompetent host. Fever, headache, photophobia and nuchal rigidity may be of variable duration and severity. Particularly in the case of subacute or chronic forms of meningitis, symptoms and findings may be subtle [20, 68]. Hence, an HIV-positive patient who presents with fever, malaise and/or nonspecific findings, even with mild abnormalities on neurologic inquiry and examination, should be investigated for CNS complications, including meningitis. This is especially important in the critically ill patient if no other cause is readily identifiable for abnormal mental status and/or the presenting condition. Given the increased likelihood of a space occupying lesion in the HIV-positive patient with neurologic abnormalities, radiologic imaging of the CNS with computed tomography (CT) or magnetic resonance (MR) is ideally recommended in all circumstances prior to performing a lumbar puncture. However, if these are not readily available, lumbar puncture may be performed safely without prior CNS imaging in patients in whom papilledema and focal neurologic deficits are absent. In any event, institution of empiric treatment should not be delayed [20].

Aseptic meningitis related to direct meningeal infection by HIV may be a presenting or complicating syndrome during seroconversion, but is more common later in the course of HIV disease as the CD4+ count falls below 250 cells/μl [20, 67]. There is associated mild cerebrospinal fluid (CSF) pleocytosis and mildly increased protein concentration. The CSF pleocytosis may respond to highly active antiretroviral therapy, but clinical benefit is uncertain [67]. Other etiologies of aseptic meningitis common to the HIV-seronegative patient are also possible and neurosyphilis should always be considered.

Acute meningitis may be due to typical agents of bacterial infection (e.g., pneumococcus, meningococcus and *H. influenza*); *Staphylococcus aureus* and *Salmonella* are also important etiologies in the setting of HIV disease. Meningitis due to *Listeria monocytogenes* may present subacutely and is more common with T-cell immune deficiency and hence in patients with HIV disease. Chronic meningitis may be due to *M. tuberculosis*, *Histoplasma*, *Coccidioides* and *Treponema pallidum* [69]. Noninfectious causes of a meningeal syndrome include lymphoma and meningeal carcinomatosis.

The most important treatable form of chronic meningitis in AIDS patients is due to *Cryptococcus neoformans*. CNS disease, a result of dissemination from the primary site of infection in the lungs, occurs as a late complication of HIV disease when the CD4+ cell count has declined below 200 cells/μl. Abnormalities of CSF may be mild or even absent; the CSF white cell count is generally less than 20 cells/μl and predominantly lymphocytic [20, 67, 68]. The serum cryptococcal antigen is highly sensitive and specific; a negative serum cryptococcal antigen virtually excludes cryptococcal meningitis [62]. Serial measurement of antigen titer in serum has not been useful in the management of infected patients and response to therapy should be based on clinical features in addition to spinal fluid culture and antigen titer. The most important predictor of early mortality is abnormal mental status at time of presentation. CSF titer greater

Presenting Symptoms: New or Worsening Headaches or CNS Dysfunction in Immunocompromised HIV-Infected Patients[1]



than 1:1024 is also associated with poor prognosis [68].

Increased intracranial pressure (ICP) is a potentially life-threatening complication in patients with HIV-related cryptococcal meningitis. In fact, early death or visual loss after the onset of chemotherapy may be related to high CSF pressure, regardless of antifungal therapy. The pathophysiologic mechanisms of increased ICP in cryptococcal meningitis are not fully understood. It has been hypothesized that absorption of CSF via the arachnoid villi is impaired due to an increased viscosity of the CSF or a microscopic plug of polysaccharide directly blocking CSF flow [70]. Symptoms consistent with elevated ICP include headache, mental obtundation, papilledema and cranial nerve palsies. An elevated opening pressure is usually defined as >200 mm CSF. In the recently reported ACTG trial [71], almost all early deaths (13 of 14) were associated with elevated intracranial pressure. Of note, patients presenting with elevated ICP do not show radiologic evidence of hydrocephalus.

Optimal therapy for this complication has not been established. In the absence of obstructive hydrocephalus, serial lumbar punctures provide a mechanism to prevent complications of a high ICP. A practical approach used in the context of the MSG/ACTG study included daily lumbar punctures, use of acetazolamide, and ventriculoperitoneal shunts for asymptomatic patients with ICP greater than 320 mm CSF and for symptomatic patients with ICP higher than 180 mm CSF. The use of lumbar drainage and selective placement of lumbar peritoneal shunts have also been attempted with satisfactory outcomes [72].

Acute meningoencephalitis is characterized by a mix of clinical meningism and CNS dysfunction (either global or focal). Potential etiologies include viruses (e.g., CMV and VZV), bacteria (such as *M. tuberculosis* and *L. monocytogenes*) and parasites (including *Toxoplasma*, *Acanthamoeba*, *Strongyloides* and *Trypanosoma*). Subacute or chronic presentation is more consistent with parenchymal and meningeal fungal infection (e.g., due to *C. neoformans*, *Aspergillus* or *Candida*). Progressive multifocal leukoencephalopathy (PML) due to CNS infection with the JC papova virus may also produce a meningoencephalitic syndrome (*vide infra*) [69].

Therapy for the various forms of meningitis is described in Table 3. Salvage therapy for crypto-

FIGURE 6. An algorithm for the management of the HIV-infected patient with headache or CNS dysfunction. History and physical examination should include neuropsychological testing where feasible. The serum cryptococcal antigen is a rapid, accurate and noninvasive method for identifying cases of cryptococcal CNS infection and a positive test should prompt initiation of therapy pending definitive diagnostic investigation. In acute toxoplasmic encephalitis, IgG is positive in 84-97% of cases, and in association with typical neuroradiological findings, may have a positive predictive value as high as 80%. Seronegative patients should be considered for early biopsy, but treated empirically in the interim for toxoplasmosis. Computed tomographic (CT; preferably with contrast) or magnetic resonance (MR) imaging should be done urgently, particularly in patients with papilledema, focal neurologic findings or seizures. If patients have an acute presentation with symptoms and signs compatible with acute bacterial meningitis, lumbar puncture (LP) should be performed without delay, provided there are no contraindications (such as papilledema or focal findings), since delay in LP and institution of appropriate therapy may affect outcome adversely. Patients presenting with headache and/or lethargy without features of acute illness should have neuroimaging performed as an initial step. However, if there is an unacceptable delay, LP should be considered, provided there are no contraindications. Multiple lesions on neuroimaging suggest toxoplasmosis, while solitary lesions indicate lymphoma, toxoplasmosis or progressive multifocal leukoencephalopthy. Empiric therapy for toxoplasmosis should be started if there are compatible clinical and neuroradiographic features. Steroids should be reserved for lesions associated with life-threatening edema. Stereotactic biopsy should be considered if there is clinical deterioration after 7 days or no response to therapy after 10 days of anti-toxoplasmic therapy. (Reproduced with permission from Tobin *et al.* (73).)

coccal disease which fails to respond to standard treatment includes liposomal amphotericin or high dose fluconazole (800–1200 mg per day) plus 5-flucytosine [20]. However, if a clear etiology is not identified readily or diagnostic testing (especially lumbar puncture) is delayed, empiric therapy should be instituted. This is especially important with regard to bacterial causes of meningitis, which are most life-threatening. Hence, empiric therapy should include high dose ceftriaxone or cefotaxime (e.g., ceftriaxone 2 g IV Q12H) and high dose ampicillin (e.g., 2 g IV Q4H). High dose vancomycin (e.g., 1 g IV Q6H) should be considered in a critically ill patient with meningitis where there is a high prevalence (>2%) of *Streptococcus pneumoniae* that has only intermediate sensitivity or resistance to penicillin. An alternative in penicillin allergic patients is combination chloramphenicol and trimethoprim-sulfamethoxazole; early penicillin skin testing is suggested. Vancomycin should also be considered in predisposed patients if there is a high prevalence of methicillin resistant *S. aureus*. In a critically ill patient with suspected meningitis and advanced HIV disease in whom lumbar puncture and serum cryptococcal assay cannot be performed in a timely fashion, empiric treatment for cryptococcosis is warranted. Therapy should be tailored based on results of microbiologic testing.

Dexamethasone 0.4 mg/kg IV Q12H for two days is suggested for bacterial meningitis, with the first dose administered with or just before the first dose of antibiotic. Development of hydrocephalus as a complication of basal meningitis (e.g., cryptococcosis, tuberculosis or listeriosis) may occur, necessitating ventricular drainage.

CNS DISEASE

Diffuse CNS dysfunction can present with depression of both consciousness and cognition (i.e., encephalopathy) or with preserved alertness in the face of cognitive impairment (i.e., dementia) [67]. In the setting of HIV infection, the latter refers to a condition termed AIDS dementia complex, which is thought likely related to primary infection of the CNS with HIV. In this condition, the CSF profile is nonspecific with normal or mild elevations of protein and mild mononuclear pleocytosis. HIV RNA viral load in the CSF is not a useful diagnostic test. The syndrome is reviewed in detail elsewhere [67].

Encephalopathy in the HIV-infected patient is usually toxic/metabolic or related to adverse medication effects. A primary encephalopathic process may be difficult to distinguish from one due to metabolic and other abnormalities typical of a critically ill patient with multiple organ dysfunction [69]. Many of the alternate causes of encephalopathy are those that cause focal CNS disease (such as toxoplasmosis or lymphoma) or meningoencephalitis. However, viral infections due to herpes simplex and CMV generally do not produce focal disease. Although herpes encephalitis is rare in the setting of HIV infection, it may be less fulminant and more diffuse [67]. CMV encephalitis can produce a syndrome indistinguishable from AIDS dementia complex, but may have a more acute encephalitic presentation. There may be diagnostic changes on neuroimaging (periventricular signal change or enhancement or HR) and the CSF profile is nonspecific, although polymerase chain reaction (PCR) of CSF for CMV may be helpful in distinguishing this process from other etiologies. Diagnosis is important, since specific therapy is available (see Table 3).

Investigation of an HIV-positive patient with a focal CNS lesion should begin with contrast CT or MR imaging of the CNS [20]. The most important etiologic considerations include the causes of meningoencephalitis, toxoplasmosis, primary B-cell lymphoma (and more rarely other neoplasms), and progressive multifocal leukoencephalopathy (PML) [67]. Other focal processes include nocardiosis, tuberculoma, neurosyphilis, fungal infection and herpes or VZV infection [20, 69]. Specific therapy is described in Table 3. A syndrome resembling multiple sclerosis also has been reported [67]. Meningoencephalitis presents with meningism as well as global or focal CNS abnormality, but depending on the

location of the lesion, all of the other conditions can present in a similar fashion. There may be differences, however, in the temporal evolution of the illness, effects on mentation, and in concomitant systemic manifestations; neuroimaging usually is most discriminating [67].

Infection with *Toxoplasma gondii* is common and 3–30% of the general population are infected [73]. Reactivation of infection with *T. gondii* leading to focal or global CNS disease is the most common infectious encephalitic process in the HIV-infected patient [67], accounting for 62% of neurologic illness on admission to ICU in one series [21] and occurring in 38% of HIV-infected persons with positive serology [73]. The disease usually occurs at a late phase of HIV disease, usually at a CD4+ count of less than 100 cells/μl [59]. Usually toxoplasmic lesions occur in the cerebral cortex or diencephalic nuclei, less often in the cerebellum, and rarely in the brainstem or spinal cord [67]; multiple lesions are more common than with lymphoma [73]. Focal deficits referable to the abscess location develop over several days. Ring-enhancing lesions with mild surrounding edema may be seen on neuroimaging [67]. Presence of serum antibody (IgG or IgM) to *Toxoplasma* raises suspicion of toxoplasmosis, particularly if a rise in titer is documented (though this is often absent in HIV disease) [69]. Diagnosis can be confirmed on biopsy, but this is rarely necessary, since a presumptive diagnosis can be established by response to therapy; only in the absence of such response does biopsy need to be undertaken to determine an alternate etiology [67]. On the other hand, negative serology should prompt early consideration of brain biopsy [20, 67]. CSF evaluation is usually risky (because of CNS mass effect of toxoplasmic abscesses) and is usually unhelpful, since standard CSF serologic testing and culture are unreliable. A PCR test now available is specific but lacks sensitivity [67]. Treatment is outlined in Table 3. The use of corticosteroids is not recommended unless edema is sufficient to be life-threatening [20, 67]. Since lymphoma may respond transiently to corticosteroids, coadministration with anti-toxoplasmic treatment may confound assessment of therapeutic response [20]. A response to therapy should be detected clinically within several days and radiologically within approximately one week [67].

The principal diagnostic alternative to toxoplasmosis in the HIV-positive patient is lymphoma. CNS lymphoma in this setting is usually primary and of B-cell origin, and virtually all lesions contain genetic material of Epstein-Barr virus [67]. The disease occurs in patients with late-stage disease at a CD4+ count less than 50 cells/μl [59, 67]. Generally, the disease progresses more slowly than does toxoplasmosis, over weeks rather than days. The lesions are usually multicentric and tend to affect the deep brain, especially in the periventricular white matter and along the subependymal surface of the lateral ventricles. Lesions appear more diffusely enhancing than toxoplasmic abscesses and there may be associated edema. If safe, CSF evaluation for cytology and PCR for Epstein-Barr virus may be helpful. PCR appears to be sensitive and specific, but if PCR is negative or not available, brain biopsy is necessary to establish a definitive diagnosis. A SPECT thallium scan may help differentiate CNS lymphoma (increased uptake) from toxoplasmosis or other brain abscess. Biopsy is usually reserved for patients who have failed anti-toxoplasmic therapy. Treatment involves radiotherapy and chemotherapy, but the prognosis is poor [67].

Opportunistic infection with the human papovavirus JC produces the clinical syndrome of PML. Infection of oligodendrocytes leads to widespread demyelination with resultant focal neurologic signs. It usually affects patients with CD4+ count less than 200 cells/μl. Onset is typically slow, over weeks to months. MR is the preferred neuroimaging modality and multiple or single lesions in the white matter are characteristic with high signal on T_2 weighting and low signal on T_1 weighting; lesions do not enhance on CT. Unlike other causes of focal lesions, there is loss of tissue rather than mass

effect. Diagnosis is usually established on clinical and radiological grounds, but PCR of CSF for JC virus sequences is specific (though not highly sensitive). Biopsy can establish the diagnosis definitively. No specific therapy exists except treatment of underlying HIV infection with combination antiretroviral medications. Prognosis is generally poor [67].

MYELOPATHY, PERIPHERAL NEUROPATHY AND MYOPATHY

Myelopathy can occur in HIV disease. This may be a vacuolar process likely due to HIV itself and resembling that found in patients infected with human T-lymphotropic virus-1 (HTLV-1) infection. It is usually diffuse and slowly progressive; there is no specific treatment [20]. Less commonly, myelopathy may be rapidly progressive and segmental with clinical transverse myelitis. Etiologic agents include CMV, VZV, *Toxoplasma* and lymphoma [20].

Subacute progressive polyradiculopathy due to CMV may cause a mix of motor and sensory abnormalities that progress over days to weeks. It is associated with abnormal CSF with polymorphonuclear pleocytosis, hypoglycorrhachia and elevated protein. CMV may be cultured or detected by PCR. Treatment is reviewed in Table 3. VZV may also produce a painful polyradiculopathy [20].

Peripheral neuropathy may occur at any stage of HIV infection. An acute or subacute demyelinating polyneuropathy resembling Guillain-Barré syndrome may occur in the HIV-infected individual, typically before there has been a marked decline in CD4+ count. This likely is an autoimmune phenomenon. Treatment with corticosteroids, immunoglobulin or plasma exchange may be beneficial [20, 67]. The disorder may be chronic [67]. A painful polyneuropathy associated with clinical features resembling Sjögren's syndrome and lymphocytic infiltration of multiple organs may also occur at the pre-AIDS stage of HIV disease; there may be response to antiretroviral drugs and corticosteroids. Similarly, a painful polyneuropathy due to vasculitis has been described and can be treated with corticosteroids [67]. The late phase of HIV infection may be associated with an axonal distal sensory polyneuropathy, possible related to HIV infection itself, although a similar syndrome may occur with some antiretroviral medications (especially didanosine, zalcitabine and stavudine). Painful dysesthesias occur in a stocking-and-glove distribution. Treatment is symptomatic [20, 67, 68].

Mononeuritis multiplex may be an autoimmune phenomenon when it occurs early in the course of HIV infection. A second type due to CMV infection occurs when the CD4+ count is severely depressed. It may affect muscles of the shoulder girdle and respiration and may be fatal if not treated early. Diagnosis may be difficult, as the CSF may be negative by culture and PCR for CMV. Anti-CMV treatment can be effective and may need to be started empirically [67].

Myopathic processes reported in the setting of HIV disease include an idiopathic inflammatory process resembling polymyositis. Corticosteroids may be of value. Infectious myopathies may also occur focally or diffusely due to toxoplasmosis or as a localized process due to *S. aureus*. Treatment is supportive and directed against the etiologic organism. Zidovudine can also induce a myositis which may be asymptomatic or present with proximal muscle weakness. Discontinuation of the offending antiretroviral agent usually results in reversal of the condition within two weeks [20, 67]. Rhabdomyolysis may also occur as a result of illicit drug use or pentamidine [74].

OCULAR DISEASE

Fundoscopy should be performed in all HIV patients when they present with acute illness. Fluffy "cotton wool" spots in the retina are common, self-limited, non-sight-threatening, and likely due to HIV itself. CMV retinitis is the most common cause of sight-threatening retinal disease. Areas of whitish exudate surrounded by hemorrhage and edema are characteristic. Treatment can forestall retinal deterioration and loss of vision [68]. A more aggressive form of retinal

necrosis affecting the outer layers of the retina (progressive outer retinal necrosis (PORN)) is also reported and is due to herpes simplex or VZ virus. Combination therapy is often needed. Consultation with an ophthalmologist is recommended.

Cardiac Disease

Cardiac involvement in HIV disease is often under-recognized [75], yet primary heart failure accounted for 5% of ICU admissions in one series [21]. Two-thirds of patients with AIDS are found to have cardiac abnormalities at autopsy and cardiovascular disease is reported in 7% of HIV-infected persons, although up to 90% of HIV-infected patients have been reported to have echocardiographic abnormalities. Cardiovascular involvement occurs in over 90% of children who have vertically-acquired HIV infection. However, clinically significant cardiac disease is generally overshadowed by involvement of other organs. Clinical cardiac disease does not affect long-term outcome, and related symptoms may be misinterpreted as being due to noncardiac causes [75, 76]. Nevertheless, primary cardiac disease may of greater importance in the critically ill HIV-positive patient. Cardiac disease may occur at any stage of HIV disease and may include endocardial (valvular), myocardial and/or pericardial involvement.

Infective endocarditis usually occurs in injection drug users and is almost exclusively bacterial and most often right-sided [75, 76]. Three quarters of cases are due to *Staphylococcus aureus*. Fungal infections with *Cryptococcus* and *Candida* are infrequent and seen almost exclusively in injection drug users [76]. Appropriate treatment is dependent on the causative organism. Where there is a high prevalence of methicillin resistant *S. aureus* in the injection drug using population, in a predisposed patient who is critically ill, initial empiric therapy with vancomycin is warranted. Endocarditis in HIV-positive persons who are not injection drug users is usually marantic (noninfectious) and this is the most frequent type of valvular involvement in patients with HIV disease. Since vegetations are sterile, valve leaflets are not destroyed and patients usually present with embolic complications [76]. Infective endocarditis due to *Salmonella* has been described in patients who do not use drugs [75]. Mitral valve prolapse can often be demonstrated on echocardiography in late-stage HIV disease, possibly the result of cachexia and loss of ventricular volume, but is not usually of clinical significance [76].

Myocarditis is found in up to 50% of HIV-infected patients at autopsy [75]. *Toxoplasma gondii* is the most common infectious cause of myocarditis in AIDS patients [76]. Other infectious etiologies include *Cryptococcus*, *Histoplasma*, *Aspergillus*, *Mycobacterium tuberculosis* and other bacteria, coxsackie B virus, Epstein-Barr virus and CMV [75, 76]. Interestingly, *Pneumocystis* seems to spare the heart [75]. HIV itself has been purported to be a cause of myocarditis, but definitive evidence is lacking [76]. Noninfectious infiltration of the myocardium has also been reported with KS and lymphoma [75]. Far more common is a nonspecific lymphocytic myocarditis, which has been found in up to 40% of cases in autopsy series, and in 80% of these cases, no etiologic agent was identifiable [75]. Despite its frequency, the relationship of myocarditis to clinical findings or functional abnormality is unclear and death related to myocarditis is rare [76]. Treatment is predicated on identification of etiology. If etiology cannot be identified, therapy is supportive.

Clinical or subclinical dilated cardiomyopathy is one of the most common cardiac complications of HIV disease [75]. Wall motion abnormalities and ventricular dysfunction are not uncommon in HIV-infected persons, but clinical ventricular failure is found in fewer than 5% of patients [76]. However, long-term survival of patients with clinical myocardial dysfunction is poor [75]. The cause of cardiomyopathy is controversial. It may be due to HIV or opportunistic infection of the myocardium, a postviral phenomenon, the result of autoimmune mechanisms

or cytokine effects, a consequence of nutritional abnormalities (such as thiamine, selenium or protein-calorie deficiency) or due to adverse drug effects (such as cocaine and potentially even nucleoside reverse transcriptase inhibitors, which are known to induce myopathy). It is most likely multifactorial. Direct HIV infection itself is felt an unlikely cause [76]. Treatment in the absence of a recognizable etiology includes standard therapy for cardiac failure, including correction of rhythm disturbances, afterload and preload reduction, digoxin and inotropes. Since primary cardiac failure due to HIV-related cardiomyopathy without identification of an underlying treatable cause that leads to need for critical care support has a poor prognosis; alteration of outcome is unlikely to be affected by ventilatory or hemodynamic support.

Pericardial involvement is the most common form of cardiac disease in the setting of HIV infection, found in 20–38% of patients [75, 76]. Most effusions are small and hemodynamically insignificant. Many are asymptomatic, but patients can present with symptoms of pericarditis or even cardiac tamponade. Most effusions are idiopathic, but may be due to infection or malignancy (including lymphoma and Kaposi's sarcoma). HIV infection of the pericardium itself may play a role [75]. Although large, hemodynamically significant pericardial effusions require drainage, small asymptomatic effusions need not be aspirated unless there is clinical evidence of systemic infection. In that case, open drainage is recommended so that pericardial biopsy can also be obtained [76]. Therapy otherwise is determined by underlying cause.

Right ventricular abnormalities and pulmonary hypertension have been reported in as many as 17% of patients. In some cases, this may represent primary pulmonary hypertension due to pulmonary vascular disease. In others, it has been linked to recurrent pulmonary infection and fibrosis [76]. Disturbances of cardiac rhythm can also occur related to medications, especially those that prolong the QTc interval on electrocardiogram (such as fluconazole, pentamidine and macrolides), which can lead to development of torsades de pointes. Malnourished patients who have hypomagnesemia are at particular risk and medications which promote renal magnesium wasting (such as pentamidine, foscarnet and cidofovir) may worsen this predisposition.

Gastrointestinal Disease

As many as 70% of HIV-positive patients develop abnormalities of the gastrointestinal (GI) tract and liver [77]. Many of these processes are chronic and may present clinical manifestations which are unrelated to the presenting critical illness (e.g., diarrhea). Indeed, Casalino *et al.* found no episodes of ICU admission related to GI disease [21]. While opportunistic and other infectious or neoplastic etiologies must be considered, diarrhea and other GI symptoms are often due to treatment effects. Hence, GI disorders are common among HIV-infected patients in the ICU setting, although they may not be the primary cause for admission.

Abdominal discomfort and GI symptoms are frequent causes of emergency room visits among HIV-infected persons [77]. Abdominal pain may be associated with common presentations, such as acute gastroenteritis, appendicitis, hepatobiliary disease, pancreatitis, perforation and obstruction. But symptoms and signs are often atypical and unusual causes must be considered, as well as multiple etiologies and non-gastrointestinal disease [78]. For example, differential diagnosis of right lower quadrant pain and tenderness must include infectious colitis (including pseudomembranous colitis) and GI perforation due to neutropenic typhilitis, CMV colitis or lymphoma. Abdominal plain radiographs, ultrasound and CT scanning are useful diagnostic modalities and endoscopic evaluation (including endoscopic retrograde cholangiopancreatography) is often essential [77, 78]. However, few HIV-positive patients require laparotomy, usually only for complications such as perforation [77].

The most common oral manifestation of HIV disease is thrush, a candidal infection of the orobuccal and lingual mucosa which may also

involve the corners of the mouth to cause cheilitis. White plaques which may be scraped away and hyphae on microscopic examination are characteristic. Topical antifungal agents or oral ketoconazole or fluconazole are usually effective therapy [68]. Oral hairy leukoplakia are pathognomonic of HIV disease and are usually observed with advanced HIV infection. Lesions are asymptomatic fine white striations on the undersurface and lateral aspects of the tongue and the condition is likely due to infection with Epstein-Barr virus. The presence of hairy leukoplakia portends a poor prognosis and predicts rapid progression of disease. There is no specific therapy, although podophyllin and desciclovir have been used with some success [68, 79].

An increased incidence of severe necrotizing gingivitis and periodontitis has also been reported [79] and may contribute to pulmonary infection through aspiration. Treatment with daily chlorhexidine mouthwashes is helpful and should be provided to all HIV-positive patients in ICU. Antimicrobial therapy may also be necessary [68, 79]. Aphthous ulceration may also occur, likely due to HIV infection itself and/or autoimmune disease. Differential diagnosis includes CMV, tuberculous and cryptococcal infections, as well as lymphoma and squamous cell carcinoma. Lesions may become secondarily infected with bacteria, especially Gram-negative organisms. Treatment of idiopathic aphthous ulceration includes fluocinonide ointment, systemic corticosteroids and thalidomide [79].

Esophageal disease is also common and up to one-third of HIV-positive patients suffer from esophageal complications. Although not usually life-threatening, esophageal disease is important in the critically ill patient, because symptoms related to esophageal conditions often contribute to antecedent poor oral intake, dehydration and malnutrition. Clinical features of esophageal disease may include odynophagia, dysphagia, singultus (hiccuping), retrosternal chest pain and bleeding [78]. In 40–80% of cases, esophagitis is due to *Candida albicans* infection, usually in conjunction with oropharyngeal candidiasis. Empiric therapy with an azole (e.g., fluconazole) is cost-effective, with further investigation or repeat biopsy if there is no response [68, 78]. If ketoconazole is used, an acid pH in the stomach is necessary for absorption; therefore, medications which raise gastric pH (such as H2 hiatomire blockers and proton pump inhibitors) should be avoided [68]. Fluconazole does not share this property, has fewer adverse effects than ketoconazole and is preferred [78]. Other imidazoles may also be used. Amphotericin B should be considered for patients with infection by a fungus resistant to imidazoles [68].

CMV esophagitis can be identified by biopsy (with relevant histopathologic changes) in 10–40% of cases. CMV may coexist with Candida in up to 20% of patients and may account for lack of response to anti-fungal therapy [78]. It may present as a diffuse esophagitis or as single or multiple ulcers [77]. Other etiologies of esophageal disease include viral infections (herpes simplex, Epstein-Barr, herpes type 6 and papova viruses, as well as HIV itself), rarely bacterial or mycobacterial disease (including nocardiosis, actinomycosis, bacillary angiomatosis (bartonellosis), and infection with *M. tuberculosis* and *M. avium* complex), pneumocystosis, protozoal disease (e.g., cryptosporidiosis) or neoplastic disease (including KS and lymphoma), as well as peptic and idiopathic aphthous esophagitis [77, 78]. Given the broad array of etiologies, endoscopic diagnosis (with tissue biopsy for culture and histopathology) in the critically ill patient is essential, particularly if empiric antifungal therapy has failed. Contrast radiography is seldom useful unless perforation is suspected, in which case CT or MR imaging of the chest (to exclude mediastinal collection) is also suggested. Treatment is determined by established etiology (see Table 3). Corticosteroids may be useful for aphthous esophagitis or in cases where no etiology is identified and there is no response to empiric therapy for common pathogens [68, 78].

In general, the stomach is prone to the same processes which affect the esophagus and there is some overlap with small intestinal disease [77, 78]. However, since *Candida* is sensitive to acid

pH, candidiasis is rarely a problem [78]. On the other hand, parietal cell dysfunction in HIV disease can lead to hypochlorhydria and overgrowth of microorganisms [78].

Interestingly, infection with *Helicobacter pylori* and peptic ulcer disease is unusual in HIV-positive persons [78]. CMV can produce extensive gastritis with abdominal pain, nausea, vomiting and even upper GI hemorrhage [68]. KS and lymphoma can result in obstruction [68]. Treatment is determined by underlying etiology (see Table 3). Of note, anti-acid medication may not be effective if there is hypochlorhydria already and sucralfate may be a better choice. Because of the high incidence of diarrhea in this population, magnesium-containing antacids are best avoided [78].

Small and large bowel disease due to malignancy or infection frequently cause GI distress in HIV-infected individuals [68]. Diarrhea occurs in at least half of patients in developed nations and up to 90% of patients in the developing world. Homosexual males and patients with CD4+ counts less than 250 cells/μl are at greatest risk [78]. History (including travel, medications and diet) is important. Infrequent or large volume stools or nocturnal diarrhea suggest a small bowel origin, while bloody or small volume, frequent stools with urgency and/or tenesmus suggest a large bowel process. Initial diagnostic investigation should include multiple stool samples for culture and sensitivity, ova and parasites, and specific tests (e.g., acid fast staining, enzyme-linked immunosorbent assay or PCR), but more intensive investigation including endoscopic evaluation has been shown to be effective [78]. Even if an enteropathogen is identified, its role in producing symptoms is not established and endoscopy is indicated [78]. Patients with symptoms suggestive of small bowel diarrhea should have upper GI endoscopy performed first, including biopsy of distal duodenum and/or proximal jejunum. If symptoms suggest a large bowel source, then lower GI endoscopy is necessary and colonoscopy is preferred, since sigmoidoscopy alone will miss a substantial proportion of lesions [78]. Given the inability to obtain history in a critically ill patient, both upper and lower GI endoscopy may be needed.

A variety of etiologic agents may be responsible. Bacterial enteropathogens, such as *Salmonella*, *Shigella* and *Campylobacter* can produce gastroenteritis with fever. Abnormalities of immune function may result in a prolonged carrier state despite antibiotic therapy [78], which has significant infection control implications in the ICU. Antibiotics are used frequently in HIV-positive patients; therefore, pseudomembranous colitis due to *Clostridium difficile* is not infrequent in this population [77, 78]. Enterotoxin production contributes to inflammation, mucosal sloughing and ulceration which may progress to toxic megacolon and perforation [77]. Since antidiarrheal agents which reduce intestinal motility can precipitate toxic megacolon, patients should not be prescribed such medication until the diagnosis has been ruled out by stool evaluation for culture and toxin assay and/or lower GI endoscopy. In late-stage HIV disease, infection of the GI tract with MAC can occur and is the likely source of disseminated infection. A diarrheal illness can also occur which can be complicated by obstruction, fistula formation, hemorrhage and perforation [78]. Treatment is the same as in immunocompetent persons and is reviewed elsewhere. Treatment of MAC infection is described in Table 3.

CMV can cause disease anywhere in the GI tract, most commonly the colon [77, 78]. Disease is due to vascular infection and inflammation with focal thrombosis, ischemia and eventual ulceration which can involve the full thickness of the bowel wall [77]. Such infection is unusual except in the advanced stages of HIV disease when the CD4+ count has declined below 100 cells/μl [78]. The diagnosis is established by careful histologic examination of multiple tissue biopsy specimens [78]. CMV infection can be life-threatening if it progresses to appendicitis with perforation and sepsis or intestinal hemorrhage, obstruction or perfora-

tion [77]. Other viral etiologies include herpes simplex virus, adenovirus, astrovirus, picobirvirus, calcivirus, coronavirus and rotavirus [68, 78]. HIV infects intestinal mononuclear cells and enterocytes, but the diagnosis of HIV-related enteropathy should be entertained only when other etiologies have been excluded, and even then, it is still considered controversial. Treatment of HIV enteropathy is symptomatic [78]. Treatment of CMV intestinal disease is described in Table 3.

Cryptosporidial infection of the small bowel occurs in 20% of HIV-positive patients in the developed world and in a much larger proportion of patients in developing nations [77]. It can occur at any stage of illness. There is better chance of spontaneous resolution in a patient with a CD4+ count greater than 180 cells/μl, but persistent exacerbations and remissions are the rule [77, 78]. At a CD4+ count less than 50 cells/μl, diarrhea may be fulminant [78]. Diagnosis is made by acid-fast stain or enzyme-linked immunsorbent assay of the stool or biopsy [78]. Microsporidiosis of the small bowel is also common, usually at an advanced stage of HIV disease. Diagnosis is generally made by biopsy [77, 78]. There is no effective treatment for either of these conditions [78]. Other protozoal pathogens of the GI tract include *Entamoeba histolytica*, *Giardia lamblia*, *Isospora belli*, and *Cyclospora cayetanensis* [78]. Appropriate therapy for these infections is reviewed elsewhere.

Other conditions involving the bowel in HIV infected persons include KS and lymphoma. These may produce chronic diarrhea and/or intestinal obstruction, but KS is the most common lesion causing upper GI hemorrhage in HIV-positive patients [77]. Hemorrhage from the GI tract is directly attributable to HIV infection in 40–60% of cases. Although the 39% mortality rate is almost five times that of non-HIV-infected patients, many lesions are treatable and an aggressive approach is warranted, including endoscopy, angiography, nuclear medicine studies and local or angiography-guided treatment, in addition to surgery [77]. Other potential causes of upper GI hemorrhage include infection (especially CMV and *Candida*), lymphoma and etiologies common in immunocompetent hosts (including esophageal varices). Lower GI hemorrhage may be due to agents of infectious colitis, KS, lymphoma and hemorrhoids [77].

Hepatobiliary disease is common and virtually all HIV-positive patients have abnormalities of liver enzymes, especially with advanced disease [78]. In addition to the usual causes of viral hepatitis, liver disease may be due to opportunistic infections. MAC infection is a particularly frequent cause, but other mycobacteria can also produce parenchymal liver disease and bacillary peliosis hepatis (due to *Bartonella henselae* or *B. quintana*) with multiple vascular lesions has also been recognized. Granulomatous hepatitis due to fungal infection occurs in advanced disease. CMV, herpes virus and adenovirus can cause hepatitis as well. Finally, *Pneumocystis*, *Toxoplasma* and rarely other protozoal agents can invade the liver. Noninfectious etiologies of hepatic disease include Hodgkin's and non-Hodgkin's lymphoma and KS, although the latter is seldom clinically significant. HIV-related medications are frequent causes of perturbations of hepatic enzymes and liver function. Up to 90% of HIV-positive patients are treated with potentially hepatotoxic agents, and often require dose reduction or discontinuation [78]. Liver biopsy may be necessary to establish the cause of parenchymal disease. Treatment is dependent on identification of the etiologic agent.

Acalculous cholecystitis has been reported and *Cryptosporidium*, microsporidia, MAC and CMV have been implicated as responsible pathogens [68, 78]. Cholangitis (AIDS cholangiopathy) occurs in more than 50% of cases with acalculous cholecystitis and immunosuppression predisposes to superimposed bacterial cholangitis [78]. Sclerosing cholangitis has also been described [77]. Biliary obstruction may also be due to compression of the bile duct by lymphoma or KS [77]. Radiologic imaging with

ultrasound or CT scanning is useful and endoscopic retrograde cholangiopancreatography is effective in the diagnosis and management of AIDS cholangiopathy, including sphincterotomy or stent placement. Cholecystitis warrants drainage or cholecystectomy [78].

Pancreatitis occurs in up to 22% of HIV-infected individuals, but most remain asymptomatic [78]. Pancreatic inflammation may be caused by medications (especially pentamidine, didanosine, zalcitabine and TMP-SMX), opportunistic infections (particularly CMV, *Cryptococcus* and *Toxoplasma*, and to a lesser extent, *Cryptosporidium*, HSV, *M. tuberculosis* and MAC), neoplasms (lymphoma and KS) and even HIV itself. The more common associations, such as ethanol use and hypertriglyceridemia (possibly secondary to protease inhibitors) should not be overlooked, especially in predisposed patients [78]. It is important to recognize that hyperamylasemia may not signify pancreatitis: macroamylasemia, due to circulating immune complexes which bind amylase, is common in HIV-infected persons [78]. Treatment of pancreatitis in the HIV-infected patient is the same as in the non-HIV-infected individual. It is imperative that offending medications be recognized and discontinued and HIV-related causes should be identified.

Renal Disease

In the setting of the critically ill patient with HIV infection, there are many potential etiologies for renal dysfunction. Acute renal failure in the HIV-infected patient is more likely to be encountered by the intensivist than chronic renal failure. Acute renal failure is due to volume depletion in one-third of cases, while 40–50% of instances are caused by drugs used to treat HIV infection or its complications, radiocontrast dye, sepsis, tubulointerstitial nephropathies, rapidly progressive glomerulonephritis and obstructive nephropathy [74].

Prerenal azotemia may lead to the development of acute tubular necrosis especially if combined with hemodynamic compromise or nephrotoxic agents. Hence, correction of volume depletion and hemodynamic support are essential, as well as identification and dosage adjustment or discontinuation of nephrotoxic drugs. Tubular necrosis may also be related to myoglobinuria due to rhabdomyolysis, which may be the result of drugs or HIV itself. Acute tubulointerstitial nephritis is usually due to medication (such as TMP-SMX, rifampin or foscarnet) and has a prognosis similar to that in non-HIV-infected persons. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) occur with increased frequency in HIV-positive patients and are discussed below. Rapidly progressive proliferative glomerulonephritis is an autoimmune phenomenon rarely seen in HIV-positive patients. Obstructive nephropathy may be the consequence of tubular precipitation of medications, such as acyclovir or indinavir, or ureteric obstruction from tumor or retroperitoneal fibrosis [74]. The outcome of acute renal failure in the HIV-infected population is similar to that of age-matched controls; 85% of patients can be managed without renal replacement therapy and approximately half of patients who require dialysis recover renal function [74].

All types of glomerular lesion have been reported in HIV disease. Chronic glomerulopathies generally occur in asymptomatic persons and the pathologic expression and outcome of renal disease is influenced by genetic, immunologic and other host factors [74]. The most common glomerulopathy is a rapidly progressive form of glomerulosclerosis [74]. This process occurs almost exclusively in blacks, and while it has been reported in otherwise asymptomatic individuals, recent evidence suggests it occurs in advanced disease and may be an AIDS defining illness [80]. The pathogenesis of the disease is unknown, but is not thought to be immunologic [74]. There is no effective treatment and all patients progress to end-stage renal failure. Prognosis of patients with renal replacement therapy is related to stage of HIV disease.

TABLE 4. Causes of cytopenias in HIV-positive patients

Anemia
Anemia of chronic disease
Parvovirus B19 infection
Adverse drug reaction
Thrombotic thrombocytopenic purpura
Hypersplenism
Marrow infiltration (infection or tumor)
Megaloblastic anemia
Autoimmune hemolysis
Iron deficiency or blood loss
Preexisting or coexisting condition
Thrombocytopenia
HIV-associated immune destruction
HIV-associated decreased production
Adverse drug reaction
Thrombotic thrombocytopenic purpura
Hypersplenism
Marrow infiltration (infection or tumor)
Leukopenia
HIV-associated lymphopenia
Neutropenia due to HIV-associated decreased production
Adverse drug reaction
Anti-neutrophil antibodies
Hypersplenism
Marrow infiltration (infection or tumor)

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The prognosis has been improved with antiretroviral therapy and the effect of highly active antiviral combinations is unknown [68, 74].

Immune complex glomerulonephritis occurs more often in white males. This condition may present with more nephritic features than glomerulosclerosis and progression to end-stage renal disease is rapid [74]. The pathogenesis may be related to immune complexes (HIV-related or due to coinfection (e.g., with hepatitis B or syphilis), a lupus-like syndrome or IgA). Again, no specific therapy exists and the outcome of hemodialytic support is related principally to stage of HIV infection [74]. Finally, nephrocalcinosis and opportunistic infection of the kidneys can contribute to chronic renal failure [68, 74].

Hematologic Disease

Hematologic abnormalities (especially cytopenias) are among the most common manifestations of HIV disease [81]. Identification of the cause of a cytopenia is important because specific therapy may be indicated. The various causes of cytopenias are listed in Table 4.

The pathogenesis of cytopenias in HIV disease is generally impaired production due to abnormalities in cytokine regulation and disturbances in the bone marrow microenvironment, as well as peripheral destruction [81]. HIV itself seems responsible for impaired hematopoiesis. Although direct infection of progenitor cells does not occur, HIV infection of marrow accessory cells may be important, perhaps by altering cytokine production [81]; these mechanisms are reviewed in detail elsewhere [82]. Given that cytopenias in HIV disease are usually not due to progenitor cell destruction and there are multiple mechanisms involved, the cellularity of the bone marrow does not correlate with the degree of cytopenia or the stage of HIV infection [81, 82]. Normal or increased cellularity is typical and dysplastic changes are common [82]. Bone marrow aspiration and biopsy can be useful in making a specific diagnosis (such as identifying bone marrow infiltrative disorders, distinguishing thrombocytopenia caused by inadequate production from that due to increased destruction, and assessing iron stores to assist in differentiation of anemia due to iron deficiency from anemia of chronic disease) [81].

The most frequent form of anemia in HIV-infected individuals is typical of anemia of chronic disease [81]. Erythrocyte production and reticulocyte count are depressed. The smear shows normochromia and normocytosis frequently with anisocytosis, and low serum iron, iron binding capacity and transferrin saturation. There are increased marrow iron stores and decreased sideroblasts. Presence of such anemia

correlates with survival from the time of diagnosis of AIDS [81]. Therapy is supportive.

Other causes of normochromic, normocytic anemia include adverse drug effects, primarily through myelosuppression (e.g., zidovudine, sulfa medications and ganciclovir). Primaquin and dapsone can induce hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency [81]. A positive direct antiglobulin (Coomb's) test has been reported, but autoimmune hemolytic anemia is rare [81, 82]. However, thrombotic thrombocytopenic purpura with thrombocytopenia, hemolytic anemia with schistocytes on peripheral smear, fever, renal dysfunction and neurological abnormalities has been reported with increased frequency in patients with HIV disease. Response to plasma exchange or plasma transfusion and antiplatelet agents is similar to that in non-HIV-infected persons [81]. Chronic pure red cell aplasia can develop in HIV-positive patients coinfected with parvovirus B19, but symptoms of fifth disease noted in immunocompetent patients are absent. The anemia responds to intravenous immunoglobulin [81]. Although serum B_{12} (cobalamin) levels are often low in the setting of HIV infection and reduced B_{12} absorption is common, patients do not generally respond to B_{12} administration [81]. Paraproteinemias, common in HIV disease, do not seem to contribute to cytopenias in HIV infection [82]. GI hemorrhage from various causes and splenic sequestration may contribute to anemia [68, 81]. Finally, bone marrow infiltration by opportunistic infection or malignancy is an important cause of anemia in the HIV-seropositive patient [68].

Treatment of anemia should be directed at the underlying cause, where one can be identified which is amenable to therapy. Otherwise, the only therapies available are blood transfusion and erythropoietin. Administration of erythropoietin may reverse suppression of erythropoiesis due to inflammatory cytokines [82]. Administration of erythropoietin has been shown to increase hematocrit and decrease transfusion requirements with improvements in quality of life in HIV-infected patients [81]. Erythropoietin therapy does not have immediate effects and is ineffective in the presence of intercurrent opportunistic infection [82]. Hence, it is not likely to be of value in the critical care setting.

Lymphopenia is characteristic of HIV infection, but is nonspecific [68]. Neutropenia is often caused or exacerbated by myelosuppressive medications used in the treatment of HIV infection, [and HIV-related complications] such as zidovudine, sulfa medications, ganciclovir and pentamidine [81]. However, the major reason for leukopenia in HIV infection is impaired production. An autoimmune neutropenia, due to circulating antineutrophilic antibodies, has also been reported and responds to high dose gammaglobulin injections [68]. Bone marrow infiltration is another important cause, usually recognized in association with other cytopenias. Where there is impaired hematopoiesis, colony stimulating factors may be effective [68]. Granulocyte-monocyte colony stimulating factor (GM-CSF) stimulates HIV replication in monocytes; granulocyte colony stimulating factor (G-CSF) does not seem to have this effect. Use of GM-CSF in combination with zidovudine may enhance antiviral effects by increasing the concentration of active drug in monocytes [82], but because of better tolerability, G-CSF is preferred [81]. Although neutropenia in HIV-infected patients seems to be better tolerated than in the setting of chemotherapy (especially with mucositis), neutropenic HIV-positive patients are prone to infection with microorganisms for which host defense is dependent on neutrophil function (*vide supra*) and appropriate isolation precautions and treatment are warranted [81].

The most important cause of thrombocytopenia in HIV is autoimmune destruction, similar to idiopathic thrombocytopenic purpura in non-HIV-infected patients, and typically occurring in the early stages of HIV disease. Antibodies are directed against the gpIIb/IIIa glycoprotein on platelets, which is similar to the gp160/120 antigen of HIV, and there is also

increased binding of immune complexes to the platelet surface. Both of these processes result in immune-mediated platelet destruction. However, nonimmune mechanisms of platelet depletion (such as consumption and sequestration) and inadequate platelet production are also important [81, 82]. Various therapeutic options are available and it is not clear which is best [82]. High dose gammaglobulin infusions raise platelet counts promptly but only transiently and repeated infusions are necessary to sustain effect [81]. Corticosteroids elevate platelet counts in 40–80% of patients, but long-term remission occurs in only 10–20% with such treatment [82]. Other therapies include vincristine and anabolic steroids, but these have an overall response rate of only 10%. High dose vitamin C and interferons have also been tried with limited success [82]. Treatment with zidovudine results in elevation of platelet counts in 40–60% and complete normalization of counts in 20%. The mechanism is unclear, although both increased thrombopoiesis and reduced peripheral destruction have been postulated [81]. As yet, other antiretroviral medications have not been shown to have this effect [82]. Finally, in patients failing other therapies, splenectomy has an initial response rate of 60–100% and long-term effect in 40–60% of patients without apparent detrimental effects [81, 82]. Splenic irradiation is an effective alternative [77].

Other mechanisms of thrombocytopenia are important in the later stages of HIV disease. These include hypersplenism and sequestration, bone marrow infiltrative disorders (especially lymphoma and opportunistic infections), thrombotic thrombocytopenic purpura, and myelosuppressive drug effects [81]. A progressive reduction in productive capacity of the bone marrow also occurs as the stage of HIV disease advances [82]. Treatment is determined by underlying etiology.

The "lupus anticoagulant" has also been reported in HIV-positive patients. This is the result of production of antibodies to acidic phospholipids, which prolongs the phospholipid-dependent clotting assay (such as the activated partial thromboplastin time). It is the consequence of the immune dysfunction characteristic of HIV disease [81, 82]. As many as 70% of HIV-seropositive patients may have such antibodies. The presence of these antibodies causes a prolongation of the partial thromboplastin time which cannot be corrected by mixing with normal plasma and may give positive results on nonspecific anti-*Treponema* serotests (e.g., VDRL) [81, 82]. Antibody titers tend to increase in the face of opportunistic infection [82]. The presence of antiphospholipid antibodies may be associated with major thromboembolic events [81, 82]. The prothrombotic state characteristic of HIV infection may also be the result of protein S deficiency, persistent opportunistic viral infections and other abnormalities of coagulation [82].

Endocrine Disease

Endocrine abnormalities are not a typical feature of HIV disease, but certain endocrinopathies encountered in HIV infection are of particular importance in the ICU [68]. The adrenal glands are most often affected, especially by infiltration with CMV, MAC, *Cryptococcus* and KS, but clinical adrenal insufficiency is uncommon. This may not be the case in the critically ill state, where relative adrenal insufficiency may have greater clinical significance, especially in patients with AIDS (who have a blunted cortisol response to adrenocorticotropic hormone). Ketoconazole interferes with cytochrome P-450 and may precipitate adrenal insufficiency, and rifampin may decrease cortisol bioavailability. A sick euthyroid state has been reported but actual clinical hypothyroidism is rare. Abnormalities of glucose can be produced with administration of pentamidine. This drug causes lysis of insulin-containing pancreatic β-cells, initially raising insulin levels and causing hypoglycemia; sustained glucose intolerance and diabetes mellitus may ensue. Medications can produce a

variety of effects on electrolyte and mineral metabolism.

Dermatologic Disease

Dermatologic disease is common in the HIV-infected patient. Multiple manifestations of infection, malignancy, autoimmunity and drug sensitivity can be found; these are reviewed in detail elsewhere [83]. The major significance of cutaneous lesions in the HIV-positive patient in the ICU setting is that they may provide clues to the cause of a systemic or more deep-seated disease process, may require specific therapy or may provide evidence of HIV disease in a patient not known to be infected.

Herpes virus infections also produce skin manifestations which are not uncommon in the critical care setting and are important to recognize [68, 83]. These include orolabial or genital herpes simplex infection, which is characterized by the presence of painful grouped vesicles on an erythematous base which rupture and become crusted. They are common and may become chronic and extensive as immunosuppression worsens. Disseminated lesions may be difficult to distinguish from VZV infection (primary [chickenpox] or secondary [shingles]) and can be differentiated by culture of vesicle fluid. Herpes virus infections are treated with thymidine kinase inhibitors (see Table 3). Acyclovir-resistant cases require treatment with foscarnet [83]. Disseminated VZV infection warrants isolation because of the possibility of airborne spread.

Common skin infections can occur with atypical presentations, such as botryomycosis (plaque or papule formation with pustules) related to staphylococcal folliculitis, sometimes with sepsis, or intertriginous impetigo [83]. Bacillary angiomatosis, due to infection with *Bartonella* species, manifests with cutaneous vascular papules (which may resemble pyogenic granulomas and may ulcerate) or subcutaneous nodules. Bone and viscera may be involved (e.g., with peliosis hepatis) and blood cultures may be positive. Bartonellosis can be differentiated from similar lesions by histopathology. Treatment with macrolides, doxycycline, TMP-SMX or quinolones is effective [83]. Other cutaneous infections include cutaneous manifestations of fungal or mycobacterial infection, syphilis or cutaneous viral exanthems, including the maculopapular rash of HIV seroconversion [83].

Noninfectious skin disorders are common. The most important disorders to recognize in the critical care setting are cutaneous drug eruptions, which are the most common manifestation of drug hypersensitivity. A variety of lesions may be seen from morbilliform eruption to Stevens-Johnson syndrome or toxic epidermal necrolysis. Antibiotics, especially sulfa medications, are the most frequent etiologies and antiretroviral agents, such as the non-nucleoside reverse transcriptase inhibitors, are also important causes [83].

Finally, neoplasms (e.g., lymphoma) can also produce cutaneous manifestations [83]. KS is an endothelial neoplasm of capillaries or lymphatics which may involve any part of the body [66] and remains a common AIDS defining illness [22]. The neoplastic process has been linked to infection with herpes virus 8, although other factors also seem to be important [64]. In the setting of HIV disease, the lesions are more common in homosexual men and are rare in other risk groups [68]. The main importance of KS in the critical care setting is that its identification should lead to a suspicion of HIV disease in a patient not known to be HIV-seropositive and that mucocutaneous KS raises the possibility that a pulmonary infiltrate or GI bleed may be due to KS as well [20].

Adverse Medication Effects

Patients with HIV disease are treated with a sometimes bewildering array of prophylactic and therapeutic agents. Many of these are associated with substantial adverse effects, some of which may be relevant to the intensivist. For example, use of TMP-SMX and other sulfa and related

drugs is common in HIV-positive patients. These medications have been linked to a systemic inflammatory response syndrome with shock which can be fatal. Associated drug eruption is a useful clue.

Increased use of antiretroviral agents has introduced new risks and potential critical illness. The development of potentially fatal lactic acidosis has been associated with the reverse transcriptase inhibitor zidovudine [84] and other nucleoside analogues [85–87]. The mechanism is thought to be nucleoside-induced mitochondrial dysfunction and alterations in mitochondrial respiration, which result in myopathy, a high lactate/pyruvate ratio, lactate accumulation, and altered fatty acid metabolism with hepatic macrovesicular steatosis [6, 84]. Hepatic failure worsens the lactic acidosis, but sepsis does not seem to play a significant role. Discontinuation of nucleoside therapy may reverse the acidosis, but may not result in recovery. The risk factors for the development of this complication have not been definitively identified. Abacavir, a nucleoside analogue, has been associated with a hypersensitivity reaction which may be fatal if the patient is rechallenged.

Protease inhibitors have been associated with a number of metabolic disturbances, particularly hyperlipidemia (including hypertriglyceridemia and low high-density lipoprotein levels) [88], insulin resistance, glucose intolerance, and new-onset or worsening of pre-existing diabetes mellitus [89]. The long-term implications of these metabolic effects are not yet known, but there have been case reports of avascular necrosis of the hip and premature coronary artery disease in patients receiving therapy with protease inhibitors. These metabolic disturbances in HIV patients on antiretroviral therapy have been associated with a syndrome of peripheral lipodystrophy and central adiposity, the etiology of which remains unclear. The associated changes in fat distribution may be of more than cosmetic significance. In a recent case in our institution, a 41-year old man with HIV and COPD experienced marked improvement in his CD4+ cell count (from 40 to 680) and suppression of his plasma viral load to undetectable (<50 copies/ml) on a regimen of two nucleosides and two protease inhibitors. However, the occurrence of abdominal obesity with thoracic adiposity further compromised his pulmonary function, resulting in his death from respiratory failure (N. Press, personal communication). Antiretroviral agents have many other side effects and toxicities; these are reviewed in Table 5.

Ethical Considerations in the Treatment of the HIV-Positive Patient in the ICU

As in other chronic illnesses, HIV-infected individuals seem not to find their disease debilitating. In one survey, 49% indicated their quality of life after HIV infection was better than before it, and patients strongly preferred longevity in their present state to reduced life expectancy in excellent health [90]. Yet, since AIDS ultimately is a fatal illness, the appropriateness of critical care for such individuals has been questioned [6].

This has been particularly so for PCP, because of the poor prognosis associated with PCP-related acute respiratory failure (ARF). Numerous studies have attempted to address the question of which patients might benefit from critical care support in this setting – or more importantly, what characteristics predict the failure of such treatment [6]. In the case of PCP-related ARF, predictors of in-hospital survival seem to be the degree of global physiological dysfunction and duration of maximal combined anti-*Pneumocystis* and corticosteroid therapy prior to development of ARF. No prognostic feature predictive of in-hospital mortality seems predictive of duration of long-term survival, and long-term survival is no different from that of patients who do not develop ARF [39]. In addition, the study by Casalino *et al.* showed no difference in functional status from baseline prior to the critical illness in HIV positive individuals who survive ICU treatment [21]. It is important also to recognize changes in the outcome of ICU

TABLE 5. Main toxicities of antiretroviral agents

Class/Agent	Toxicities
Nucleoside analogues	All agents in this class: Liver dysfunction, lactic acidosis, hepatic steatosis,
Zidovudine	Macrocytic anemia, neutropenia, nausea, vomiting, headache, rash, myopathy (with elevated CPK), nail pigmentation
Didanosine	Hyperamylasemia, pancreatitis, peripheral neuropathy, diarrhea, nausea, vomiting, hyperuricemia, gout, sicca syndrome
Zalcitabine	Peripheral neuropathy, mouth ulcers, rash, pancreatitis
Stavudine	Peripheral neuropathy, paricreatitis
Lamivudine	Anemia, neutropenia (both rare)
Abacavir	Hypersensitivity reaction[1]
Nonnucleosides	All agents in this class: Rash, Stevens-Johnson syndrome or erythema multiforme (rare), elevated transaminases, hepatitis
Nevirapine	Methadone withdrawal, somnolence
Delavirdine	Nausea, vomiting
Efavirenz	CNS disturbance[2], methadone withdrawal
Protease Inhibitors	All agents in this class: Peripheral lipodystrophy syndrome[3], bleeding episodes in hemophiliacs, liver dysfunction
Saquinavir	Gastrointestinal intolerance, headache
Ritonavir	Gastrointestinal intolerance, taste disturbance, circumoral and/or peripheral paresthesias, headache, hypertriglyceridemia, hepatitis, elevated CPK and uric acid
Indinavir	Gastrointestinal intolerance, benign hyperbilirubinemia, dry skin and lips, nephrolithiasis, crystal nephropathy
Nelfinavir	Diarrhea, abdominal pain, rash
Amprenavir	Diarrhea, rash, paresthesias

[1] Abacavir hypersensitivity is rare (3%) and potentially fatal. Symptoms may include fever, rash, malaise, nausea, vomiting, diarrhea, headache, fatigue, chills, myalgia, and respiratory symptoms (dyspnea, pharyngitis, cough). In cases of suspected hypersensitivity reaction, abacavir should be discontinued. Rechallenge should not be attempted, as it has been associated with life-threatening reactions and death.
[2] Efavirenz is associated with a usually transient disturbance of sleep and/or mood in 52% of patients during the first 4 weeks on therapy. Symptoms include dizziness, light-headedness, impaired concentration, somnolence, insomnia, abnormal dreams, confusion, agitation, depression, depersonalization, or hallucinations.
[3] A syndrome of peripheral lipodystrophy has been associated with protease inhibitor containing regimens, with prevalence rates ranging from 25 to 84%. Features include peripheral subcutaneous fat loss and central fat accumulation, hypercholesterolemia, hypertriglyceridemia, insulin resistance, and (rarely) hyperglycemia.

treatment for PCP (and other HIV-related illness) over time, which reflect changes in treatment strategy, general patient care, patient selection and demographics or comorbidities [39].

Recent investigations have attempted to address the outcome of non-PCP critical illnesses in HIV-infected individuals. For instance, in one study, as with PCP and other critical illnesses, in-hospital mortality for non-PCP critical illness was related to severity of organ dysfunction on presentation and the duration of AIDS diagnosis prior to ICU admission. Markers of severity of immunosuppression were not predictive of short-term survival. On the other hand, long-term survival was dependent only on the severity of underlying AIDS [91]. Similarly, Casalino

et al. found short-term, in-hospital mortality (39%) was comparable to that of non-HIV infected patients admitted to ICU [21]. Further, across all categories, functional status among survivors was similar to that prior to their critical illness. The investigators also showed that in-hospital mortality is related to severity of physiologic organ dysfunction on admission to ICU and the nature of presenting illness (lowest for respiratory (34%) and miscellaneous (such as drug reactions and overdoses and renal failure; 24%) groups; highest for neurologic (41%), cardiac (69%) and sepsis (58%) groups). Duration and severity of AIDS prior to ICU was also predictive of short-term outcome, but CD4+ count was not. In addition, HIV-related variables (other than CD4+ count) were associated with long-term survival [21]. However, the severity of AIDS as a determinant of outcome is difficult to judge in the present era and previous antiretroviral use is likely of greater significance [6].

Despite refinements in the development of prognostic tools, they are not sufficiently predictive to direct decision making in the individual patient. Furthermore, respect for patient autonomy dictates that patient values be paramount in the decision making process. Preliminary results of a decision analysis suggest that these values are important in the decision making of patients, particularly with regard to advanced directives. While the values patients place on outcomes are important in determining treatment choices where there is an intermediate chance of survival, in this model of rational decision making, those values become exponentially less influential on the favored decision where the chance of survival is very poor [92]. This implies that other values, such as consideration of efficient use of costly resources, may become more important [6]. Defining the risks and benefits of ICU care where outcome is less certain is thus especially important in assisting patients to judge the value of such support and help in their decisions about its institution [6, 21].

Thus, it is important to recognize that outcome from critical illness in the setting of HIV disease dose not render provision of such support futile. Indeed, given documentation of good long-term outcomes in many situations and the improved prognosis for those suffering from HIV disease, critical care support for HIV-positive patients may not just prolong life but also may preserve good quality of life. As with any chronic illness, the worth patients place on their life quality should not be underestimated. It is paramount that patients' wishes and values should be sought and respected in decisions about their medical care.

Conclusions

In spite of reductions in mortality due to HIV disease as a consequence of powerful antiretroviral regimens, changing demographics and increasing infection rates suggest HIV-positive patients will continue to require ICU support, so that the relevance of HIV disease in critical care medicine will not diminish. While the spectrum of critical HIV disease likely will change, respiratory failure related to PCP undoubtedly will remain an important reason for ICU admission. However, HIV-related illness in the critical care setting has protean manifestations affecting virtually every organ system. Furthermore, new drug-related diseases are likely to become an increasing problem. Thus, the intensivist must maintain a familiarity with the clinical features of HIV disease as they may appear in the critically ill HIV-positive patient. Such knowledge is also important in recognizing manifestations of HIV-related illness in the patient who is not known to be infected, so that appropriate therapy can be provided.

The degree of physiologic dysfunction in multiple organ systems in particular is an important predictor of in-hospital mortality of ARF due to PCP, and for other HIV-related illnesses requiring ICU admission. The duration of maximal combined anti-*Pneumocystis* and corticosteroid therapy in PCP prior to ICU admission is also an important determinant of short-term outcome. The long-term survival of patients

with ARF due to PCP is comparable to that of patients with PCP who do not develop ARF and variables predictive of in-hospital mortality do not predict long-term survival. In general, long-term survival of AIDS patients who require ICU admission is largely determined by the stage and progression of their underlying HIV disease, but this is difficult to ascertain in the modern era of highly active antiretroviral therapy. Importantly, the functional status of patients who survive ICU appears similar to their baseline prior to developing critical illness. Hence, as more is learned of the evolving spectrum and outcomes of critical illness in HIV disease, such knowledge should inform a discussion between patients and their caregivers about the circumstances, role and desirability of critical care support.

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