Critical care of immunocompromised patients: Human immunodeficiency virus

Mark J. Rosen, MD; Mangala Narasimhan, DO

Objective: **To describe critical illnesses that occur commonly in patients with human immunodeficiency virus (HIV) infection.**

Methods: **We reviewed and summarized the literature on critical illness in HIV infection using a computerized MEDLINE search.**

Summary: **In the last 10 yrs, our perception of HIV infection and acquired immune deficiency syndrome (AIDS) has changed from an almost uniformly fatal disease into a manageable chronic illness. Even patients with advanced immunosuppression may have prolonged survival, although usually with exacerbations and remissions, complicated by therapy-related toxicity and medical and psychiatric co-morbidity. The prevalence of opportunistic infections and the mortality have decreased considerably since early in the epidemic. The most common reason for intensive care unit admission in patients with AIDS is respiratory failure, but they are less likely to be admitted for *Pneumocystis* pneumonia and other HIV-associated opportunistic infections. HIV-infected persons are more likely to receive intensive care unit care for complications of end-stage liver disease and sepsis. Hepatitis C has emerged as a common cause of morbidity and mortality in patients with HIV infection. In addition, some develop life-threatening complications from antiretroviral drug toxicity and the immune reconstitution inflammatory syndrome. (Crit Care Med 2006; 34[Suppl.]:S245–S250)**

KEY WORDS: human immunodeficiency virus; HIV; acquired immune deficiency syndrome; AIDS; intensive care; antiretroviral therapy; respiratory failure; outcomes; highly active antiretroviral therapy

The first cases of acquired immune deficiency syndrome (AIDS) were reported in the United States in 1981 when a group of gay men with no known underlying disorders developed *Pneumocystis* pneumonia (PCP) (1). In the 1980s, AIDS was considered to be uniformly fatal, and questions on the benefits of aggressive interventions in the intensive care unit (ICU) arose for each patient with advanced disease. Respiratory failure due to PCP was by far the most common disorder that prompted ICU admission, and outcomes were uniformly dismal. The AIDS epidemic has evolved continuously since the early years, and these changes are reflected in the care of patients with human immunodeficiency virus (HIV) infection in the ICU. AIDS was initially considered to afflict mainly gay men, but now in the United States, HIV is transmitted predominantly through injection drug use and heterosexual contact, especially among racial and ethnic minority populations.

The AIDS epidemic grew to be an international catastrophe, with >20 million deaths worldwide by the end of 2004, and three million deaths in 2004 alone (2, 3). The outlook for HIV-infected persons has improved immensely in countries where there is ready access to treatment with combinations of antiretroviral agents (previously known as highly active antiretroviral therapy, or HAART) (4). Since the use of these drugs became the standard of care in 1996, U.S. mortality rates due to AIDS declined from an annual high of around 45,000 per year to the current plateau of around 18,000 (2, 5). In the last 10 yrs, our perception of HIV infection and AIDS has changed from an almost uniformly fatal disease into a manageable chronic illness (5, 6). Nevertheless, in many urban communities and in underdeveloped nations, AIDS-related illnesses are still among the leading causes of death among young adults.

It still is not known if the benefits of HAART in reducing HIV-associated morbidity and mortality are reflected in reduced ICU admission rates, different diagnoses, or better outcomes for HIV-infected persons who develop life-threatening illness. Before the use of HAART, respiratory failure was the most common reason for ICU care, and it was usually due to PCP (7). Many people with HIV infection are treated in ICUs for HIV-associated disorders other than PCP and for critical illness unrelated to HIV infection, including gastrointestinal hemorrhage, cardiovascular disease, sepsis, trauma, drug overdose, and disorders of the central nervous system. A few studies indicate that in the era of HAART, ICU admissions for PCP have declined, and overall outcomes seem to be improved. Patients may also become critically ill from the toxic effects of antiretroviral medications and from an accelerated inflammatory response related to immune reconstitution accompanying the use of HAART.

Reasons for ICU Admission

The literature on the frequency and reasons for ICU admission in patients with HIV infection must be interpreted with the understanding that with rare exception, each study reviews the experience of a single center and reflects local ICU admission criteria and practice patterns. Care of patients with HIV infection and with critical illness in general may vary widely, so the conclusions of these

From the Division of Pulmonary and Critical Care Medicine, Beth Israel Medical Center, New York, NY (MJR, MN); and the Department of Medicine, Albert Einstein College of Medicine, New York, NY (MJR).

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Table 1. Human immunodeficiency virus–associated respiratory disorders

Bacterial pneumonia
Streptococcus pneumoniae
Haemophilus influenzae
Pseudomonas aeruginosa
Staphylococcus aureus
Moraxella catarrhalis
Rhodococcus equi
Mycobacterium tuberculosis
Nontuberculous mycobacteria
Fungal infections
Pneumocystis jiroveci
Cryptococcus neoformans
Histoplasma capsulatum
Aspergillus fumigatus
Coccidioides immitis
Blastomyces dermatitidis
Protozoal infections
Strongyloides stercoralis
Toxoplasma gondii
Viral infections
Cytomegalovirus
Adenovirus
Herpes simplex
Malignancies
Kaposi's sarcoma
Lymphoma (Hodgkins and non-Hodgkins)
Carcinoma of the lung
Other disorders
Sinusitis
Bronchitis
Bronchiectasis
Emphysema
Lymphocytic interstitial pneumonitis
Nonspecific interstitial pneumonitis
Bronchiolitis obliterans organizing pneumonia
Pulmonary hypertension
Immune reconstitution syndromes

reports cannot be generalized (8). The decision on whether to admit HIV-infected patients to the ICU or withhold such treatment varies by hospital characteristics (county/state, Veterans Affairs Medical Centers, church-affiliated, voluntary, and for-profit) and geographic location, and these differences are maintained after controlling for severity of illness and patient demographic and socioeconomic characteristics. Thus, data on diseases and outcomes from one center cannot be applied reliably to others. Endemic fungi and other pathogens influence ICU admission rates for different diseases; this may be important in the United States, where the epidemic has shifted from the east and west coasts to the southern states (2).

Before the use of HAART in the United States and Europe, an estimated 5–10% of hospitalizations of patients with HIV infection involved an ICU admission; most patients were admitted for respiratory failure, and PCP was the most common diagnosis (9, 10) (Table 1). PCP was consistently the most common cause of respiratory failure, but it seems that ICU admissions for PCP have declined in recent years (11, 12). The few published studies of intensive care in the era of HAART suggest that overall ICU utilization by HIV-positive persons has not declined and that respiratory failure is still the most common reason for admission. However, patients are less likely to be admitted for PCP and other HIV-associated opportunistic infections. Rather, patients are now more likely to have life-threatening sepsis, neurologic disorders, and complications of end-stage liver disease (13–15). HIV-infected patients are more likely to be admitted to the ICU with problems unrelated to HIV infection or with conditions related to antiretroviral therapy (16).

Pneumocystis Pneumonia

Pneumonia caused by *Pneumocystis jiroveci* (formerly classified *Pneumocystis carinii*) has always been a major cause of illness and death in patients with HIV infection. Once thought to be a parasite, genomic analysis revealed that *P. jiroveci* is in fact a fungus that infects only humans, whereas *P. carinii* is pathogenic only in immunodeficient rats. Despite the change in taxonomy of this pathogen, the term PCP is still acceptable shorthand for *Pneumocystis p*neumonia.

Although immune restoration from HAART and effective specific chemoprophylaxis for PCP have existed for years, this infection still occurs for several reasons: many patients do not know that they have HIV infection until they develop an opportunistic infection, others know that they have HIV but are not receiving medical care, and some are in care and are not prescribed prophylaxis or HAART (17). Adherence to complex regimens with intolerable side effects is often problematic, and the development of resistant strains of HIV is common. Some patients take prophylaxis for PCP but are still so profoundly immunocompromised that it is ineffective (18). Nevertheless, the prevalence of PCP has declined in the era of HAART and is reflected in the reduced rates of ICU admission for this infection (19).

The diagnosis of PCP is established by identification of the organism in specimens obtained from the respiratory tract, either in sputum induced by inhalation of hypertonic saline or by bronchoscopy (20). Although establishing a diagnosis is not difficult, many clinicians treat patients with suspected PCP empirically, reserving bronchoscopy for patients who do not respond to treatment. Decision-analysis modeling of these two strategies suggests that the outcomes are similar, but there has not been a clinical trial that evaluated whether initial empirical therapy or a more aggressive diagnostic strategy is preferable (21).

Trimethoprim-sulfamethoxazole is the preferred treatment for PCP in patients who have not had an adverse reaction to this drug (22). Patients with severe PCP who do not respond or who are intolerant of this medication are usually given pentamidine, but this drug is associated with adverse reactions that are more serious than those associated with trimethoprim-sulfamethoxazole. Trimetrexate-leucovorin is not as effective as trimethoprim-sulfamethoxazole but is better tolerated than pentamidine (23). Whether it should replace pentamidine as a second-line treatment of moderate to severe PCP is unknown, as comparative trials of these two drugs have not been performed.

When treatment of PCP is delayed or ineffective, patients may develop hypoxemic respiratory failure. The clinical and radiographic features of severe PCP resemble the acute respiratory distress syndrome, with hypoxemia, intrapulmonary shunting, reduced pulmonary compliance, and diffuse radiographic opacities (Table 2) (24). As the disease progresses and pulmonary compliance diminishes, pneumothorax is common, and is associated with a particularly poor prognosis (Fig. 1) (25, 26). Just as severe PCP resembles acute respiratory distress syndrome clinically, the supportive treatment is similar, including intubation, mechanical ventilation, and application of positive end-expiratory pressure.

Animal models of PCP indicated that the clinical severity of infection correlates more closely with markers of inflammation than with the burden of organisms, suggesting that the immune response and its attendant inflammation account for the clinical manifestations of pneumonia (27). Respiratory compromise is associated with the presence of activated $CD8^+$ cells and neutrophils in the lung, and corticosteroids are thought to lessen these effects, but the mechanism of action is unclear. In patients, adjunctive corticosteroid therapy given at the start of anti-*Pneumocystis* treatment reduces the likelihood of respiratory failure, deterioration of oxygenation, and

Table 2. Human immunodeficiency virus infection: Chest radiographic patterns and common pathogeneses

Focal infiltrates
Bacteria
Mycobacterium tuberculosis
Pneumocystis jiroveci (uncommon)
Diffuse opacities
P. jiroveci
M. tuberculosis
Kaposi's sarcoma
Bacteria
Disseminated fungal infection
Cytomegalovirus
Diffuse nodules
Kaposi's sarcoma (large nodules)
M. tuberculosis (miliary nodules)
P. jiroveci
Fungi (small nodules)
Pneumothorax
P. jiroveci
Mediastinal lymphadenopathy
M. tuberculosis
Nontuberculous mycobacteria
Kaposi's sarcoma
Lymphoma
Fungi
Pleural effusion
Bacterial (parapneumonic or empyema)
M. tuberculosis
Kaposi's sarcoma
Lymphoma
Fungi
Cardiomyopathy
Hypoproteinemia
Cavitation
M. tuberculosis (high $CD4^+$)
Pneumocystis carinii (low $CD4^+$)
Pseudomonas aeruginosa (low $CD4^+$)
Rhodococcus equi
Fungi

death in patients with moderate to severe pneumonia (28). Gas exchange typically deteriorates during the first few days of anti-*Pneumocystis* therapy when corticosteroids are not given; corticosteroids may attenuate lung injury caused by the inflammatory response to killed organisms, allowing the patient to survive to receive more antimicrobial therapy (29). Patients likely to benefit have a Pao_2 of <70 mm Hg or an arterial–alveolar oxygen difference of >35 mm Hg. There is no benefit associated with corticosteroids in patients with less severe abnormalities in gas exchange at the start of therapy or in whom corticosteroids were administered for >72 hrs after anti-*Pneumocystis* treatment was begun.

Some patients with PCP are admitted to ICUs but do not receive mechanical ventilation. The reasons for admission may include performance or complications of bronchoscopy, application of continuous positive airway pressure by mask, or for observation that cannot be achieved with routine floor care. These patients would be expected to have a better outcome than those who have more severe respiratory impairment, and published studies confirm that they do (30).

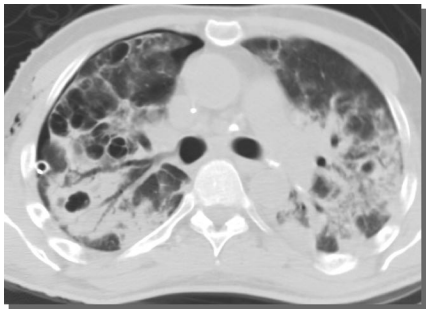

Figure 1. Selected computerized tomographic image of a patient with severe *Pneumocystis* pneumonia. This patient has significant cystic changes and areas of dense pulmonary consolidation. Note the pneumothorax and chest tube in the right lung.

To counsel patients or their surrogates on whether to forgo or discontinue mechanical ventilation, it would be helpful to define predictors of "futility," for which the survival rate is close to zero. There are no reliable predictors of futile treatment for PCP. A multiple-center trial of corticosteroids for PCP showed that survival after 2 wks of mechanical ventilation was unprecedented, but the cohort only consisted of 22 of 251 patients with PCP who received mechanical ventilation, of whom 11 survived (31). This number is too small to support the conclusion that ventilatory support for >2 wks is futile, and other centers have contradictory experience (32).

Before the availability of HAART, patients who survived mechanical ventilatory support for PCP rarely lived for >1 yr. With the use of HAART, the prospects for long-term survival are considerably more hopeful, especially if the patient has not yet received antiretroviral therapy (33). Therefore, although the likelihood of surviving an episode of respiratory failure due to PCP may warrant pessimism, the prospect of long-term survival with HAART should be considered in counseling patients and their surrogates on the desirability of starting or continuing mechanical ventilatory support. These decisions must always take the patient's preferences and premorbid condition into account.

Co-infection with Hepatitis C and HIV

Simultaneous infection with HIV and hepatitis C virus (HCV) has had a major effect on mortality in recent years, with HCV-related deaths becoming more common after improved HIV treatment with HAART (34–36). An estimated 15–30% of patients with HIV are co-infected with HCV, and the prevalence of HCV is up to 93% in injection drug users (37). HIV-infected persons tend to have more severe liver disease and liver-associated mortality than HCV-infected persons without HIV disease. Death rates from HCV increased after the introduction of HAART, and the prevalence of HCV-associated cirrhosis is four times higher in patients with HIV infection compared with HIV-seronegative persons (38–40). It seems that impaired cellular immunity from HIV infection leads to accelerated HCV reproduction, with an eight-fold increase in HCV replication in HIV-infected persons compared with HIV-seronegative persons. Conversely, HCV also accelerates the progression of HIV disease (41). Management of co-infection with HIV and HCV should include agents active against both viruses, but the timing and optimal combinations present problems related to pharmacodynamics and toxicity.

Immune Reconstitution Syndromes

When HAART inhibits viral replication, there is a corresponding increase in the population of memory and naïve T cells, enhancement of lymphoproliferative responses, increased interleukin-2 receptor expression, and reduced production of some plasma cytokines (42). These proinflammatory effects underlie newly recognized syndromes associated with immunologic reconstitution, some involving the lung. These disorders are grouped as the immune reconstitution inflammatory syndrome, or IRIS. Diagnostic criteria for IRIS include the diagnosis of AIDS, treatment with anti-HIV medications, symptoms consistent with an infectious or inflammatory condition that occurred while receiving antiretroviral therapy, and symptoms that cannot be explained by a newly acquired infection or by the expected clinical course of the disease or side effects of therapy.

In the lung, some patients develop a granulomatous disorder that resembles sarcoidosis, whereas others with latent or active mycobacterial infection may develop fever, lymphadenopathy, and opacities on the chest radiograph 2–8 wks after starting treatment with HAART (43, 44). IRIS may not be associated with an

increase in circulating T-lymphocytes because these cells are compartmentalized to areas of active inflammation; nevertheless, the syndrome should be considered in any patient who has been recently started HAART, with worsening symptoms. IRIS may be severe enough to cause respiratory failure. In one series, three patients developed worsening respiratory failure after HAART was introduced during treatment for PCP (45). These patients had severe PCP and developed acute respiratory failure 7–17 days after starting HAART (1–16 days after being diagnosed with PCP). Bronchoalveolar lavage and lung biopsy specimens showed severe immune and inflammatory reactions. The patients all improved after discontinuation of HAART, reintroduction of corticosteroids, or both. IRIS has also been described after or during infection with *Mycobacterium avium* complex, cryptococcosis, cytomegalovirus, herpes zoster, hepatitis B and C viruses, and the agent that causes progressive multifocal leukoencephalopathy.

Toxic Effects of HAART

The protease inhibitors and nucleoside analog reverse transcriptase inhibitors used in HAART may carry the risk of life-threatening toxicities that prompt admission to the ICU. Protease inhibitors may cause pancreatitis, which may be severe. In a retrospective study of 73 HIV-infected patients with pancreatitis, 46% of cases were attributed to drug toxicity (46). Protease inhibitors also cause a syndrome of lipodystrophy, insulin resistance, and hyperlipidemia (47). It is unknown if this syndrome will eventually lead to excess mortality from complications of atherosclerosis, and treatment with lipid-lowering agents is problematic because of interactions with protease inhibitors (48).

Nucleoside reverse transcriptase inhibitors may cause lactic acidosis by disrupting mitochondrial DNA replication by selective inhibition of DNA polymerase-γ. This in turn may cause hepatic steatosis, lactic acidosis, or mitochondrial myopathy (49, 50). Lactic acidosis is the consequence of increased anaerobic glycolysis by damaged mitochondria, coupled with decreased lactate clearance by the fatty liver. Mild hyperlactemia occurs commonly in patients receiving nucleoside analog reverse transcriptase inhibitors and is not clinically important, but severe lactic acidosis occurs at a rate of 1.3 cases per 1,000 person years of nucleoside exposure and may be life threatening (51–53). The initial symptoms are nausea, profuse vomiting, and abdominal pain followed by hyperventilation, liver failure, and finally, arrhythmias. Because patients may also develop severe lactic acidosis due to sepsis, empirical antibiotics are administered pending the results of a bacteriologic evaluation. If severe hyperlactemia or lactic acidosis is found, then the nucleoside analog reverse transcriptase inhibitor should be stopped immediately, and standard supportive care should be given. Case reports suggest that this disorder may improve with riboflavin, L-carnitine, and coenzyme Q (54, 55).

Abacavir is a nucleoside analog that is used in HAART regimens. It is highly potent, with good bioavailability and central nervous system penetration. However, it is also associated with hypersensitivity reactions within a few weeks of treatment in around 3% of patients, and rechallenge often leads to life-threatening anaphylaxis (56, 57). The initial hypersensitivity reaction is characterized by fever, chills, nausea, diarrhea, and rash. The rash is not always present, sometimes misleading the clinician into diagnosing an infection. However, the anaphylactic reaction to rechallenge is diagnostic, with cardiovascular collapse and high fever. The treatment is supportive, and death is common despite these measures.

Management of Prophylaxis and HAART in Critically Ill Patients

If an HIV-infected patient develops a critical illness, prophylaxis against opportunistic pathogens like *P. carinii* should be started or continued unless it is otherwise indicated. However, the decision to start HAART during or shortly after a critical illness or a severe infection is problematic. Proponents of early institution of HAART, even in critically ill patients, hold that prompt and effective treatment of underlying HIV infection is the most important determinant of long-term survival and that an improved immune system would facilitate the resolution of an active infection that prompted the ICU admission in the first place. However, these drugs are often difficult to administer to critically ill patients. Only zidovudine is available in an intravenous preparation; others must be taken on schedules that take into account normal meals.

All of the antiretrovirals may have significant interactions with other medications that may be used to treat the critical illness, and drugs may impose new toxicities in patients not well enough to withstand them. In addition, immune reconstitution after antiretroviral therapy may lead to a new life-threatening accelerated inflammatory response to active or resolving infection, as in the cases of respiratory failure after institution of HAART in patients recovering from PCP. Clearly, more studies must be performed to determine the optimal timing of HAART in patients with or recovering from serious illness. For these reasons, most clinicians defer starting HAART until the acute illness has resolved or improved significantly. Patients already receiving HAART should continue to receive these drugs whenever possible, as discontinuing therapy is associated with viral replication and the emergence of resistance. In these cases, the critical care clinician is well advised to manage these patients in close collaboration with an expert in antiretroviral treatment.

Predictors of Outcome

Overall, it seems that critically ill patients with HIV infection have similar short-term outcomes as other patients with a comparable severity of illness (58–60). However, outcome studies in patients with HIV infection are limited by a selection bias, as they were retrospective analyses in which the admitting physicians knew the patients' serostatus. A study performed in a South African surgical ICU was conducted in which all patients who were admitted were tested for HIV infection without their consent. Neither the clinicians nor the patients learned the results of the HIV test unless a staff member obtained a needle-stick injury or a patient required hemodialysis (59). At discharge, the patients were informed that they were tested and given the option of learning the test results. Posttest counseling was offered when the test results were disclosed. A total of 52 of the 402 patients (12%) admitted to the ICU had HIV infection; none had Centers for Disease Control–defined AIDS. None of these patients were admitted for an HIV-related disorder, and there were no differences in ICU or hospital mortality or stay when the results were adjusted for age, despite a higher prevalence of sepsis and organ failure in the HIV-infected patients. It is also of interest that only three

of the 402 patients tested wanted to know the results of their HIV test and that no patients objected to being included in the study without their consent. Despite the methodologic and ethical issues this study raises (and that the authors acknowledge), it supports the concept that HIV-infected persons have similar outcomes of intensive care as uninfected patients and that decisions regarding the appropriateness of ICU interventions should not use HIV status alone as a criterion.

Studies examining the value of laboratory tests and scoring systems in predicting ICU outcomes, including lactic dehydrogenase, serum albumin, $CD4^+$ lymphocyte count, Acute Physiology and Chronic Health Evaluation II score, and multiple-system organ failure scores yield conflicting data on their reliability. No measurement is sufficiently predictive to make firm conclusions on whether intensive care will be effective for an individual patient (26, 61). It is clear that patients with HIV/AIDS do not have a worse short-term outcome than other patients with a similar severity of illness. Long-term survival is related to the severity of the HIV disease, other co-morbid illness, and whether the patient has been treated with HAART. Because the outcome of intensive care does not depend directly on the patient's HIV status, serostatus and $CD4^+$ lymphocyte counts should not be overriding considerations in deciding whether to offer or withhold intensive care. Rather, these decisions should be made using the same criteria as for all patients, namely, the likelihood of benefit and the patient's wishes. In addition to the patient's illness, the experience of the hospital and healthcare providers in treating HIV infection and its complications also influences mortality. In one large study, adjusted mortality for patients with AIDS was 30% lower among hospitals with the most experience treating these patients (62). Overall, the outcomes for patients with HIV infection admitted to the ICU who do not have respiratory failure is better than for those who do (10, 12, 13, 63, 64).

Summary

The prevalence of AIDS-related opportunistic infections and the mortality from AIDS has decreased considerably since the pre-HAART era. ICU admissions are still most commonly for respiratory failure but are less likely to be for PCP. HIV-infected patients are more likely to be admitted to the ICU for complications secondary to end-stage liver disease, neurologic disorders, and sepsis than for HIV-associated opportunistic infections. There is a very high prevalence of co-infection of HIV with hepatitis C, and as a result, liver disease has emerged as a common cause of morbidity and mortality in patients with HIV. Other important reasons for ICU admission in patients who are HIV infected are complications related to the toxic effects of HAART and from IRIS.

The evolution of the AIDS epidemic and the introduction of effective antiretroviral therapy imposes many new questions about the types of life-threatening disorders that patients with HIV infection develop, their outcomes, and the best ways for us to counsel and treat our patients. A multidisciplinary, multiple-center study of critical care of patients with HIV infection would yield valuable insights. Until the important clinical questions are answered, the critical care clinician should work closely not only with the ICU multidisciplinary team but also with colleagues with backgrounds in infectious diseases, pharmacology, and palliative care.

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