Approach to Imaging Pulmonary Disease in the Immune Compromised Host

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Abstract: The increasing number and variety of patients with compromised immune systems poses a diagnostic challenge for the chest physician. Manifestations of pulmonary disease on imaging studies are diverse, with substantial overlap possible between entities. This article reviews radiologic findings in common disease states encountered when treating immune compromised patients and provides a framework for approaching common imaging manifestations, such as air-space consolidation, ground-glass opacities, and nodules.

Key Words: immune compromise, chest radiology, HIV/AIDS

Patients who have compromised immunity present a challenge to the chest physician. Causes of immune compromise are varied and include intrinsic disorders of the immune system, acquired diseases such as infection with human immunodeficiency virus (HIV), and medical therapies such as post-transplant immunosuppression. The spectrum of pulmonary diseases in these patients is broad and varies with the type and degree of immune compromise. Although the most frequent clinical concern in this population is for infections, disorders associated with immune compromise range from noninfectious inflammatory diseases to malignancies. Radiologic studies play an important role in diagnosis and must be reviewed with consideration for the immune deficiency of the host. In this article, we review mechanisms of immune compromise, common infectious and noninfectious diseases in immune compromised patients, and key radiologic patterns as a foundation for an organized approach to radiologic findings in this diverse and challenging patient population.

Mechanisms of Immunity and Immunodeficiency

An immunocompromised host is conventionally defined as a patient with decreased function of the immune system, resulting primarily in a decreased resistance to infection. There are 3 main groups of immunocompromised patients: those with congenital defects in immunity, those with acquired defects in the immune system, and those with defects secondary to medical therapies, which suppress an otherwise normal immune response. Understanding the mechanisms of normal and disordered immunity is an important step toward understanding the diseases that occur in patients with immune compromise.

Host defenses can be divided into 3 basic categories. First are physical barriers such as skin and mucous membranes. Second is cellular immunity, including phagocytes, neutrophils, natural killer cells, T lymphocytes, and macrophages. Third is humoral immunity consisting of the complement cascade, lysozymes, interferons, interleukins, and immunoglobulins. Each of these defenses can be altered by genetic defect, disease, or immunosuppressive therapy.

Specific deficiencies in immunity are associated with specific pulmonary diseases. Neutropenia, a cellular immune deficiency commonly associated with post-transplant immunosuppression, bone marrow transplantation, and chemotherapy, occurs when levels of circulating neutrophils fall and is most pronounced when the absolute neutrophil count falls below 500/μL. Typical infections in the setting of neutropenia include those caused by gram-positive bacteria such as Staphylococcus aureus and Streptococcus pneumoniae, and gram-negative bacteria such as Escherichia coli, Klebsiella species, and Pseudomonas species. Fungal infections with Aspergillus and Candida species are also common. Hereditary causes of neutrophil defects include Chediak-Higashi disease (an autosomal recessive defect in lysozyme function), and chronic granulomatous disease.

The most common acquired defect in cellular immunity is infection with HIV, which leads to impairment of cell-mediated immunity from both natural killer and cytotoxic T cells and a decreased humoral response. The incidence of pulmonary infection increases as the number of CD4 T lymphocytes fall. T-cell deficiency results in infections with organisms such as Mycobacteria, Pneumocystis jiroveci, Cryptococcus neoformans, S. pneumoniae, and viruses such as cytomegalovirus (CMV) and human herpes virus 8 (associated with Kaposi sarcoma). Congenital defects in cellular immunity include severe combined immunodeficiency disease, DiGeorge syndrome, and Wiskott-Aldrich syndrome.

Humoral immune deficiencies result from impaired antibody production caused by defects either in B cells themselves or the interaction between B and T cells. Humoral
immunity defects include congenital defects such as X-linked agammaglobulinemia, and acquired defects caused by B-cell malignancies such as chronic lymphocytic leukemia, multiple myeloma, and non-Hodgkin lymphoma. These patients have recurrent sinus, pulmonary and systemic infections, typically from encapsulated bacteria such as S. pneumoniae and Hae-
mophilus influenzae.1,2

Immunosuppression with corticosteroids, chemother-
apapeutic agents, and other immunosuppressive agents make up another large category of immunocompromised pa-
tients. Corticosteroids have multiple effects including in-
hibiting cytokine production, secretion of inflammatory
factors, and reducing T-cell activation and proliferation,
leaving to defects mainly in cellular immunity. Other
drugs such as cyclosporine, azathioprine, mycophenolate,
tacrolimus, antitumor necrosis factor antibodies, and anti-
lymphocyte antibodies block various specific pathways
required for lymphocyte activation.2,3

Inborn diseases that compromise barriers to infection
such as immotile cilia syndrome and cystic fibrosis also make
up an important group of patients with immune deficiencies.
In the adult population, however, it is more common to
encounter acquired immunodeficiencies.

HIV/AIDS in the Era of Highly Active
Antiretroviral Therapy

Changing Pattern of Disease With Highly Active
Antiretroviral Therapy

Patients with HIV and acquired immunodeficiency syn-
drome (AIDS) may be considered as 2 subpopulations. Pa-
tients who are taking highly active antiretroviral therapy
(HAART) with prophylactic antibiotics have seen a dramatic
decrease in mortality and pulmonary morbidity, whereas
those who do not have access to or do not take these
medications continue to have a high incidence of opportuni-
tic infections and other conventional manifestations of HIV.
One large series of 1538 patients demonstrated that HAART
decreased the incidence of PCP by 35%, Kaposi sarcoma by
34%, and cryptosporidiosis by 60%.4 Mocroft and col-
leagues5 reported a reduction of 39% in the incidence of KS
between 1994 and 2003 in the EuroSIDA cohort. As more
patients are treated with HAART, a different set of clinical
entities has emerged because of the short- and long-term
suppression of HIV, such as immune reconstitution inflam-
matory syndrome, lymphoma, and pulmonary hypertension.
Pulmonary diseases, however, remain the main cause of
morbidty and mortality in patients with HIV, with or without
treatment.4,6,7

Relationship to CD4

The epidemic of HIV/AIDS has largely defined the role
for imaging in the immunocompromised patient. The types of
infection seen in the HIV/AIDS population vary as the degree
of immune compromise increases. Knowledge of the CD4
lymphocyte count is therefore an important part of the history
in these patients. As the CD4 count falls below normal levels,
patients experience a higher risk of bacterial pneumonia.

With CD4 counts below 500/µL, patients become increas-
ingly susceptible to bacterial pneumonias and postprimary
tuberculosis (TB). With CD4 counts below 200/µL, the
threshold for AIDS, P. jiroveci becomes the most common
cause of pneumonia in absence of prophylaxis, although
bacterial pneumonia is still frequent. Primary tuberculosis is
increasingly seen. With CD4 counts below 100/µL, toxoplas-
mosis, nocardiosis, cryptococcosis, and atypical appearances
of tuberculosis are seen. Viral infections with CMV and
herpes simplex viruses become more common.8–10 Thoracic
Kaposi sarcoma generally is seen with CD4 counts below
100/µL.11 Non-Hodgkin lymphoma may occur at any CD4
level, but increases with falling CD4 counts, particularly
below 100/µL, where relative risk to patients with normal
CD4 levels has been reported to reach 11.2,12

Immune Reconstitution Inflammatory Syndrome

It is increasingly recognized that treatment of AIDS
with HAART can result in mild-to-severe worsening of
underlying pulmonary disease, classically in the setting of
latent mycobacterial infection.13–16 This is associated with
immunologic recovery and is termed immune reconstitution
inflammatory syndrome (IRIS), sometimes referred to as
immune restoration or immune reconstitution disease. The
mechanisms underlying the syndrome are not fully under-
stood, and there is no universally agreed-upon definition, but
some consensus as to unifying features is emerging. The
syndrome typically occurs in patients infected with AIDS and
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With patients who were previously infected with M. tuberculosis and
have a significant virologic response to treatment, with de-
crease in viral load and increase in CD4 count. Drug-resistant
infection, adverse drug reactions, or newly acquired infec-
tions are not considered part of the syndrome, and attempts
should be made to exclude them.

At least 20 infectious agents have been linked to IRIS,
including Mycobacteria, C. neoformans, P. jirovecii, hepatic
and CMV. IRIS has been linked to sarcoidosis, Kaposi sarcoma, and anal carcinoma. Specific
features of IRIS depend on the latent disease. Fever is a
common clinical manifestation seen in most cases. The most
common pulmonary causes are Mycobacterium tuberculosis and
Mycobacterium avium complex, accounting for up to
40% of cases. Radiographic findings in the setting of tuber-
culosis include lymphadenopathy, pulmonary nodules, and
pleural effusion, although consolidation and hepatosplenomegal
have been described. In M. avium complex, IRIS
most commonly presents as fever and lymphadenitis. Ex-
trathoracic nodes may be involved, and unusual cases of soft
tissue abscesses and osteomyelitis have been reported.14–19

In general, treatment for IRIS consists of initiation of
treatment of the underlying pathogen, corticosteroid or other
anti-inflammatory administration to suppress inflammation,
and in severe cases, cessation of HAART.13,15–17,20–22

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Specific Infections in HIV/AIDS

Pneumocystis Pneumonia

*P. jirovecii* (formerly *P. carinii*) pneumonia remains the most common opportunistic infection in patients with HIV/AIDS, although there are reports in some populations on HAART of bacterial infections becoming more prevalent. This organism, now considered a fungus rather than a protozoan, is an AIDS-defining illness in HIV infection. *Pneumocystis* uniquely targets the lung, where it exists primarily as an alveolar pathogen, although disseminated infection in severe immunocompromise is known. Symptoms of infection typically include low-grade fever, progressive dyspnea, and nonproductive cough. Among AIDS patients with *Pneumocystis* pneumonia, mortality rate is 10% to 20%, thus early identification is critical. Typical features on chest radiography consist of bilateral perihilar ground-glass air-space opacities that become increasingly widespread (Fig. 1). Indistinct centrilobular nodules are sometimes present. Geographic patchy opacities may occur, and a “crazy paving” appearance (ground-glass opacity associated with interlobular septal thickening, often with sharp, nonanatomic demarcations between normal and abnormal lung) has been described. Pattern of distribution can be altered by aerosolized pentamidine prophylaxis, in which upper lobe predominant disease is seen, because of the distribution of the inhaled medication. With progression of infection, pneumatoceles are frequently seen, favoring the upper lobes. Pneumothorax in the setting of AIDS is most commonly caused by *Pneumocystis* pneumonia. Cysts are useful in distinguishing PCP from other causes of ground-glass opacities. Consolidation is atypical, occurring in about 10% to 12%. High-resolution CT has greater sensitivity for detecting infection, which often is manifested by diffuse ground-glass opacities not visible on plain radiographs. Pleural effusions and lymphadenopathy are unusual findings. Although CXR may often be normal in 10% to 20% of patients with PCP, abnormality is almost invariably present on HRCT, and a normal HRCT effectively excludes *Pneumocystis* pneumonia.

Tuberculosis

Infection with HIV is the most important risk factor for development of tuberculosis, and tuberculosis is the leading opportunistic infection and cause of death in HIV-infected patients worldwide. The association of tuberculosis with HIV/AIDS, in part, accounts for the resurgence of tuberculosis in the late 20th century. Diagnosing tuberculosis infection is complicated by the high incidence of negative skin tests because of failing cell-mediated immunity and the increased likelihood of normal chest radiographs. HIV infection may be associated with development of drug resistance, although the association between multidrug resistant TB and HIV seems to largely represent an effect of the susceptibility to transmission of drug resistant TB in HIV patients.

Patterns of radiographic abnormalities differ in the setting of HIV/AIDS, depending on the degree of immune compromise. In the absence of significant depression of CD4 levels, tuberculosis presents as it does in the non-HIV population. Patchy consolidation predominating in the upper lobes and superior segment of the lower lobes is most common, with cavitation in about half of patients. Tree-in-bud type centrilobular nodules with branching opacities from bronchiolar inflammation is also frequent, likely caused by endobronchial spread of infection. As CD4 counts decrease, particularly below 200/μL, CT findings are those of primary TB, regardless of prior exposure to TB. Lymphadenopathy becomes the dominant feature of presentation, often with central low density consistent with necrosis. Central necrosis is suggestive of tuberculosis, but can be seen in other infections and malignancies such as squamous cell carcinoma. The presence of visibly enlarged lymph nodes on CXR in HIV-positive patients with CD4 counts of less than 200/μL suggests tuberculosis. Disseminated disease, in the form of miliary tuberculosis, is also more common. Miliary disease is generally not associated

![FIGURE 1. A, Frontal chest radiograph of a 51-year-old man with AIDS (CD4 count 81/μL) demonstrates diffuse ground-glass opacities caused by *P. jirovecii* pneumonia. B, Axial thoracic CT image confirms diffuse ground-glass opacities. Note that these opacities do not obscure pulmonary vessels.](image-url)
with lymphadenopathy and random nodules may also be seen with concomitant confluent nodules and consolidation (Fig. 2).\textsuperscript{38,40} Once treatment for tuberculosis is started, there may be transient worsening in the radiographic appearance caused by immune reconstitution inflammatory syndrome. In the absence of evidence, clinical or radiographic for response, infection with multidrug resistant tuberculosis should be considered.

**Nontuberculous Mycobacteria**

Nontuberculous mycobacteria are common environmental organisms of varying pathogenicity, distinct from *M. tuberculosis* and *Mycobacterium leprae* (the causative agent of leprosy). Atypical mycobacterial infections are AIDS-defining illnesses. *M. avium complex* is the most common atypical mycobacterium in the setting of immune compromise, and disease presents differently than in the immunocompetent host. Clinical features include fever, night sweats, and weight loss. The syndrome of middle lobe and lingular bronchiectasis and tree-in-bud nodules or upper lobe cavitation should not be expected. These patients usually present with hilar and mediastinal lymphadenopathy as the dominant finding. Hilar masses can mimic bronchogenic carcinoma, and may be asymptomatic (Fig. 3). Also seen are diffuse pulmonary opacities including small centrilobular nodules and areas of air-space consolidation.\textsuperscript{39,43} Pleural effusion and cavitation are uncommon.\textsuperscript{38} *Mycobacterium kansasi* infection is uncommon, particularly since the advent of HAART, and is associated with CD4 counts below 50/\mu L. *M. kansasi* frequently presents with heterogeneous air-space opacities or nodules, and may cause cavitation. Lymphadenopathy is less prominent. Miliary disease is very unusual.\textsuperscript{44-48}

**Nonmycobacterial Bacterial Pneumonia**

Bacterial pneumonias increase in frequency as CD4 counts fall. Bacterial pneumonia is at least 6 times more
frequent in the patient with AIDS than in the general population (Fig. 4). Most bacterial pneumonia is community-acquired, with *S. pneumoniae* being the most common organism isolated. Clinical presentation of pneumococcal pneumonia is similar in the setting of HIV. *H. influenzae*, *S. aureus*, *E. coli*, and *Pseudomonas* species account for most other cases. Although consolidation is the most frequent imaging finding, as in the non-AIDS population, atypical patterns including nodules and ground-glass opacities occur frequently, and there is an increased incidence of cavitation, effusion, and empyema. The presence of an ipsilateral effusion should increase suspicion for bacterial infection. *Nocardia* should also be considered in the setting of cavitating nodules and consolidation, and also often presents with pleural effusion.39,46,49,50

Some unusual bacterial infections are seen almost exclusively in the setting of AIDS. *Rhodococcus equi* is a gram-positive rod associated with soil and animal manure. Although the first reported human infection was of the skin in a renal transplant patient, it is now recognized as a rare cause of pneumonia in patients with AIDS. Patients present with cough and fever, and imaging most commonly reveals segmental consolidation and cavitation, that may resemble tuberculosis. Small centrilobular nodules with “tree-in-bud” configuration or mediastinal adenopathy are also frequently present. Pleural effusion is unusual.51–56 *Bartonella henselae*, the cause of cat-scratch disease (bacillary angiomatosis), can on rare occasions also cause pulmonary infection in the patient with AIDS. Pulmonary nodules and were first reported, subsequently endobronchial nodules and lymphadenopathy have been described.57–59

**Non-PCP Fungal Pneumonias**

*Cryptococcus* is the most common fungal infection in patients with AIDS, particularly with CD4 counts of less than 100/μL. Although the peripheral nodule typical of infection in the nonimmunocompromised host can occur, atypical patterns are common findings on thoracic CT in the immune compromised population, including segmental or lobar consolidation, patchy airspace opacities, masses, multiple nodules with a tendency to cavitate, and miliary disseminated disease (Fig. 5). Lymphadenopathy is seen in about one-third of patients, but tends to be mild. *Candida* pneumonia is associated with random nodules, with nodules seen in up to 95% of patients. Although *Pneumocystis* pneumonia is a risk factor for mycetoma, *Aspergillus* infections tend to be rare in the setting of HIV infection and will be discussed in the setting of organ transplantation.39,60–63

**Viral Pneumonias**

Viral pneumonias typically occur in the setting of severe suppression and reduction in CD4 cells below 50/μL. These are discussed below in the section on organ transplantation.

**Parasitic Infections**

AIDS constitutes one of the major risk factors for parasitic pulmonary infection in industrialized countries, although parasitic infections remain a rare cause of pulmonary disease.64 Pulmonary infections with *Toxoplasma gondii* and *Cryptosporidium* have been reported in patients with severe immune suppression in the setting of AIDS and organ transplantation, although the role of organisms isolated from lungs in the setting of infection is not well defined. Ground-glass opacities and interstitial opacities are reported, with progression to acute respiratory distress syndrome described.65–67 *Strongyloides stercoralis*, an intestinal nematode usually associated with mild pulmonary symptoms such as cough, can cause fulminant respiratory illness in the setting of immune compromise (Fig. 6). Hyperinfection syndrome occurs with massive infection and widespread dissemination of *Strongyloides* larvae, and causes ARDS with diffuse pulmonary opacities. Diagnosis is made by serologic testing or isolation of the organism from the GI tract or pulmonary aspirates.68,69
Noninfections Pulmonary Complications of HIV/AIDS

Kaposi Sarcoma

AIDS-related Kaposi sarcoma is the most common of 4 main variants of Kaposi sarcoma. Kaposi sarcoma is the most common tumor in AIDS patients, and is an AIDS-defining illness, although incidence has fallen with the advent of HAART. Kaposi sarcoma is a systemic illness with frequent pulmonary involvement. Patients typically present with cough, fever, and dyspnea. Thoracic disease is found in about 45% of patients with mucocutaneous disease, whereas only about 15% of cases occur in the absence of mucocutaneous findings. Imaging features on high-resolution CT include peribronchovascular interstitial thickening and irregular “flame shaped” or ill-defined nodules also in a peribronchovascular distribution (Fig. 7). Lymphadenopathy and pleural effusion may be present. Median survival has been reported as 1.6 years from time of diagnosis.

Lymphoma

Patients with HIV have an increased incidence of lymphoma, which along with Kaposi sarcoma and cervical cancer, is an AIDS-defining malignancy. The lung is frequently involved in AIDS-related lymphoma. This most commonly is of an aggressive B-cell non-Hodgkin type. Although lymphoma risk is elevated in patients with non-HIV related immunosuppression, rates are generally higher in the setting of HIV. In an early study of CT findings in 38 patients with thoracic lymphoma, nodules (50% of patients), lobar infiltrates (27%), and lung masses (19%) were the most common parenchymal findings, with a large number of patients having pleural effusions (68%) and thoracic lymphadenopathy (54%). Multiple nodules and masses 1 to 5 cm in diameter are typical (Fig. 8). Peribronchovascular thickening may be seen because of tumor infiltration of the interstitium. This pattern can mimic Kaposi sarcoma. Rates of non-Hodgkin lymphoma have fallen since the introduction of HAART, but not as dramatically as with some other HIV-associated diseases.

Non-AIDS-Defining Malignancies

Several malignancies are linked to HIV/AIDS in addition to the AIDS-defining malignancies described above. In a review of cancer registries identifying 375,933 patients with AIDS, Engels et al noted lung cancer to be the most common non AIDS-defining malignancy. Other reported diseases associated with immune suppression include cancers of skin, liver, breast, and prostate. It is postulated that defects in cell-mediated immunity caused by HIV result in decreased tumor surveillance by the immune system, and increased...
susceptibility to oncogenic viruses. It is not clear whether the risk is directly associated with suppression of CD4 lymphocyte counts. Like Kaposi sarcoma and non-Hodgkin lymphoma, rates of lung cancer have decreased since the introduction of HAART; however, the rate of Hodgkin lymphoma has increased in the past decade.

**Interstitial Lung Disease**

Interstitial pneumonitis can occur in the setting of HIV. Lymphocytic interstitial pneumonitis has a demonstrated association with HIV infection, and is particularly common in children. There is a reported predominance in patients of African descent. Radiographic findings are not specific, and diagnosis relies on biopsy. Typical high-resolution CT findings include ill-defined centrilobular nodules and ground-glass opacities, with thickened and sometimes nodular peribronchovascular interstitium (Fig. 9). The early literature in AIDS referred to a nonspecific interstitial pneumonitis that occurred in the setting of AIDS with clinical features resembling *Pneumocystis* pneumonia but without detectable infection, with diffuse alveolar damage and variable interstitial inflammation on transbronchial or open lung biopsy. These reports in the 1980s predated NSIP as first described by Katzenstein and Fiorelli in 1994 and differ from the histopathologic description currently recognized in the American Thoracic Society/European Respiratory Society consensus classification of idiopathic interstitial pneumonias. It is therefore likely that the early description of a nonspecific interstitial pneumonitis in AIDS reflected a common inflammatory reaction to an unrecognized infection or inflammatory process distinct from the idiopathic pneumonia presently designated NSIP.

**Pulmonary Hypertension**

Pulmonary hypertension is seen with increased incidence in patients with HIV, without correlation with severity of HIV infection. No predisposing factor other than HIV infection is found in a majority of cases. Patients present with symptoms and signs including chest pain and progressive dyspnea. Chest radiographs and CT may demonstrate dilated pulmonary arteries and right chamber cardiac enlargement. Prognosis is poor, with mean survival in the Swiss HIV Cohort Study Group of 2.7 years. Recent studies suggest survival is improved with HAART.

**Emphysema in HIV**

Emphysema has been shown to occur with increased incidence in HIV-positive patients. In a study of 114 HIV-positive patients in whom other pulmonary complications of AIDS were excluded, Diaz et al. found that when compared with age, sex, and smoking history matched HIV-negative volunteers, incidence of emphysema was higher (15% vs. 2%) and of increased severity. Bronchoalveolar lavage in a subset of these patients demonstrated a higher concentration of lymphocytes in the setting of HIV infection. In non-HIV infected smokers, there have been reports of a high correlation between such lymphocytes and emphysema, and thus viral activation of lymphocytes in the lungs of patients with HIV is thought to contribute to lung destruction.

**Organ Transplantation and Immune Suppressive Therapy**

Organ transplantation relies on an increasing pharmacologic ability to suppress host immune response as a means of preventing tissue rejection. However, the same immune suppression that permits organ engraftment exposes the recipient to potential complications including post-transplant infection, lymphoproliferative disorders, and an increased risk of certain cancers. Cancer therapy may also result in immune suppression.

**Lung Transplantation**

Lung transplantation for pulmonary or systemic diseases has been performed in over 13,000 patients in the past...
10 years and continues to gradually increase in frequency, with 1815 transplants reported in 2004 among 158 centers participating in the registry of the International Society for Heart and Lung Transplantation.\textsuperscript{88} Infection is the most common cause of morbidity and mortality following lung transplantation, with infectious complications accounting for at least half of deaths. Most infections involve the respiratory tract, and infection is also a risk factor for development of bronchiolitis obliterans, which is the primary manifestation of chronic rejection. Bacterial infection is most common, with overall incidence during the first year after transplant of about 70%. \textit{Pseudomonas} species, \textit{Enterobacteraceae}, \textit{S. aureus}, and \textit{H. influenzae} predominate.\textsuperscript{89} The complex interplay of events in transplantation ranging from initial postoperative recovery to long-term suppression of rejection result in a temporal pattern of pulmonary diseases.\textsuperscript{90,91}

In the first week after transplantation, the most common causes of radiographic opacities are reperfusion pulmonary edema, volume overload, infection, or acute rejection. Radiographic findings are nonspecific and include diffuse or peripheral opacities with occasional patchy airspace consolidation. Although pleural effusion is common, persistent or worsening effusions suggest acute rejection or infection. Acute rejection manifests histologically as perivasculare and interstitial mononuclear infiltrates, and radiographically as new or worsening airspace opacities. Acute rejection often occurs in the first 5 to 10 days after transplantation, and is treated with high-dose steroid administration. Early acute rejection cannot be distinguished radiographically from reperfusion edema and volume overload. Absence of ground-glass opacities on high-resolution CT is useful for excluding moderate or severe rejection.\textsuperscript{35,62,63}

In the first month after transplantation, bacteria are the most common cause of pneumonia, and risk of bacterial infection is highest in the first 3 months. Infection may occur via transmission with the donor organ, or from a nosocomial source. Typical patterns of opacification on CT include consolidation, ground-glass opacification, and nodules. After 1 month, opportunistic infection with CMV, the second most common cause of infection, or fungus becomes more common. Nodules are typically seen in CMV and fungal infection, but as with bacterial pneumonia, ground-glass opacification and consolidation are common in both entities.\textsuperscript{35,90}

Beyond 1 year, infections remain an important cause of morbidity and mortality; however, bronchiolitis obliterans (obliterative bronchiolitis) is the most common cause of death. Bronchiolitis obliterans is a manifestation of chronic rejection, and typically develops 6 to 12 months after transplantation. Patients present with progressive dyspnea and dry cough. Radiographic assessment is very useful in suggesting the diagnosis, as transbronchial biopsy has limited sensitivity. Air trapping demonstrated on expiratory high-resolution CT is the most sensitive radiographic feature, and may be accompanied by bronchiectasis. Severity of involvement clinically is measured by declines in FEV\textsubscript{1} on pulmonary function testing.\textsuperscript{88,90,92,93} Although less common, malignancies including PTLD (post-transplantation lymphoproliferative disorder) also should be considered when more than 1 year from transplantation. Malignancy contributes to as much as 10% of deaths in the period exceeding 1 year after transplantation.\textsuperscript{88,91}

CT is useful to evaluate patients following transplantation, both for detecting immediate complications including bronchial or vascular complications, and for evaluating the wide range of other infectious, inflammatory, and neoplastic processes that can occur.\textsuperscript{94} In post-transplant patients, there is substantial overlap in the appearance of bacterial, viral, and fungal pneumonias, limiting specificity. Bacterial pneumonias tend to have consolidation in almost all cases, with a high incidence of associated ground-glass opacities and frequent nodules.\textsuperscript{95} Nodules or masses following transplantation suggest infection, including bacterial, fungal, or mycobacterial, but bronchogenic carcinoma and PTLD also must be considered in the later post-transplant period. Pulmonary nodules occur in approximately 10% to 12% of lung transplant patients, typically in the transplanted lung. Multiple nodules may be caused by Aspergillus, Nocardiosis, CMV pneumonia, bronchiolitis obliterans, and metastases. When found in the native lung, nodules should raise the prospect of bronchogenic cancer, particularly in the setting of pulmonary fibrosis.\textsuperscript{96} Solitary nodules also favor cancer and PTLD. Cavitation suggests \textit{Aspergillus}, other fungal infection, or \textit{Nocardia} (Fig. 10).\textsuperscript{97}

\textbf{Aspergillus}

\textit{Aspergillus} infection is most commonly caused by \textit{Aspergillus fumigatus}, \textit{Aspergillus flavus}, and \textit{Aspergillus niger}.\textsuperscript{98} \textit{Aspergillus} manifestations are typically seen in the setting of neutropenia, and vary with degree of granulocyte dysfunction, ranging from aspergillomas and allergic bronchopulmonary aspergillosis to airway invasive \textit{aspergillus} and angioinvasive \textit{aspergillus}. Colonization occurs in up to 85% of lung transplant recipients, with invasive disease occurring in up to 26%, with averages in a recent review of pooled patients from the literature of 26% with colonization and 5% with invasive aspergillosis.\textsuperscript{89,99}

\textbf{FIGURE 10.} Axial thoracic CT image of a 59-year-old man who underwent left lung transplant demonstrates multiple nodules, including this right lung nodule with central cavitation (arrow). Note the relative lucency of the native lung caused by emphysema. \textit{Nocardia} was isolated.
Aspergillomas occur in preexisting cavities within lung tissue, most commonly in patients with a history of tuberculosis, sarcoidosis, or PCP, and is usually present in patients without immune compromise although a series in patients with HIV has been reported. Allergic bronchopulmonary aspergillosis is a hypersensitivity disease also occurring in immunocompetent patients, classically presenting with upper lobe bronchiectasis with mucus impaction, often of high density.

Semiinvasive aspergillosis, also known as chronic necrotizing aspergillosis, occurs in patients with disorders that mildly compromise host immunity, typically diabetes, alcoholism, or chronic obstructive pulmonary disease. Semiinvasive aspergillosis causes local invasion of lung tissue and is an indolent process that progresses over months. Typical imaging findings include segmental consolidation in the upper lobes or the superior segments of the lower lobes, sometimes with cavitation, with adjacent pleural thickening.

Airway invasive aspergillosis and angioinvasive aspergillus occur in frankly immunocompromised patients with neutropenia or AIDS. Airway invasive disease causes tracheal and bronchial thickening, but often radiologic studies are normal. Centrilobular nodules or tree-in-bud appearance may be present from bronchiolitis. Angioinvasive aspergillosis is an aggressive infection that occurs in patients with severe immune compromise. Major risk factors include prolonged neutropenia or intrinsic neutrophil dysfunction, high-dose corticosteroid therapy, transplantation (especially of lung or bone marrow), AIDS, hematologic malignancy, or chemotherapy. Patients typically present with fever, cough, pleuritic chest pain, and hemoptysis. Characteristically, x-rays are nonspecifically abnormal with patchy consolidation and nodules. On CT, nodules with a rim of surrounding ground-glass opacity, the “halo sign,” suggest the diagnosis, and represent hemorrhagic infarcts caused by vascular invasion (Fig. 11A). The halo sign can be seen on occasion with other fungal diseases such as Mucor and Candidal infection, as well as CMV and HSV, Wegener’s granulomatosis, and Kaposi sarcoma. Amphotericin B and itraconazole are employed for treatment, but response is variable and mortality is significant. Confirmation of diagnosis should be pursued, as mortality is high and mucormycosis is often managed surgically. Lung resection has also been proposed in some cases of invasive pulmonary aspergillosis in patients with neutropenia.

Two variants of the “air crescent” sign exist. An aspergilloma may be associated with a rim or air crescent between the mass and the wall of the cavity. Such aspergillomas are typically mobile. In patients with more severe immune deficiency and angioinvasive aspergillosis, there is a second air crescent seen when lung necrosis occurs because of vascular invasion (Fig. 11B). As lung cavities and necrotic lung consolidates, a rim of air can be seen forming an air crescent. The air crescent in angioinvasive disease tends to occur several weeks after infection and is associated with improved survival.

Post-transplantation Lymphoproliferative Disorder

PTLD is an important consideration in transplant recipients. Most common in patients with lung transplants, it occurs in all transplant populations, including both solid organ and bone marrow, with an overall incidence of 1% to 10%. Mortality is estimated at 40% to 70%. PTLD accounts for approximately 3% of deaths in lung transplant recipients in the first year after transplant. Most cases occur within 2 years of transplantation, with median time to onset of 6 months in solid organ recipients. Presently, the development
suggests that PTLD results from infection of B-cells by Epstein-Barr virus with subsequent proliferation in the setting of compromised T-cell immunity. High levels of immune suppression, in particular with antilymphocyte therapy, increases the risk of disease. Thoracic PTLD typically presents as solitary or multiple well-circumscribed solid masses or nodules, up to 5 cm in size (Fig. 12). These tend to occur in the mid and lower lungs, with peribronchovascular distribution. Growth is slow, and a subtle halo of ground-glass opacity may be seen. Lymphadenopathy is variably present. Less common are consolidation, ground-glass opacity, endobronchial lesions, or pleural effusion. Patients with focal disease do better than those with widespread disease, and disease outside the chest is frequent.35,90,91,104,105

**Bone Marrow Transplantation**

Bone marrow transplantation is used to treat hematologic malignancies and some tumors. Transplantation of autologous harvested marrow or donor marrow typically occurs after ablation of native host marrow. As in solid organ transplantation, the chronologic course of immune system ablation and reengraftment is useful in predicting the likely causes of infection in such patients, and follows a similar course. The first month following transplant, during which time patients are usually neutropenic, is characterized by susceptibility to organisms such as gram-negative bacterial infection, Candida infection, and Aspergillus infection. Pulmonary edema and drug toxicity may present as diffuse ground-glass opacities, diffuse alveolar damage, and hypersensitivity pneumonitis.106 Engraftment is signaled by an increase in absolute neutrophil counts above 500/µL. The following period, to 100 days after transplant, is the early postengraftment phase. CMV is a frequent pathogen. CMV pneumonia occurs in up to 15% of bone marrow transplant patients 1 to 3 months following transplant, and will be discussed further to follow.107 Toxoplasmosis is a rare parasitic infection occurring in up to 1% of patients undergoing allogenic transplant, with presentation averaging 59 days after transplant in one large study.108 Rare cases of fatal ARDS in early postengraftment toxoplasma pneumonitis have been reported.65 Beyond 100 days, a reconstituted immune system is expected, although the host is still susceptible to possible complications such as graft-versus-host disease. Bacterial infection remains a risk, particularly to community-acquired organisms, whereas risk of opportunistic infection is reduced.109,110

**CMV and Other Viral Pneumonias**

CMV pneumonia is a herpes virus that occurs as an opportunistic pathogen in patients with impaired cellular immunity. CMV infection occurs most commonly in the setting of lung transplantation, bone marrow, and other organ transplantation, with rates typically between 53% and 75% but reported as high as 90%.89,111,112 Clinical presentation includes fever, cough, and hypoxemia. Infection in the setting of immune compromise is likely caused by reactivation of latent infection.113 Incidence has been reduced by antiviral prophylaxis.89,114 Radiographic findings are typically bilateral, and include ground-glass opacities in 66% to 69%, ground-glass opacities or poorly marginated centrilobular nodules in 59% to 69%, and lobular or patchy areas of consolidation in 31% to 59%, with combinations of these patterns frequent (Fig. 13). No specific finding alone is characteristic, but the combination of findings in the correct clinical context is suggestive.115–118

Other viral pneumonias encountered in the immunocompromised host include respiratory syncytial, varicella-zoster, herpes, adenovirus, influenza, parainfluenza, and measles viruses. As in CMV infection, the lungs histologically show diffuse alveolar damage with hemorrhage, edema, lymphocyte infiltration, and hyaline membrane formation. There is significant overlap of radiographic appearance among viral infections. Typical manifestations include poorly defined small centrilobular or random nodules and patchy areas of peribronchial ground-glass opacities with patchy consolida-
Chemotherapy agents with resulting pneumonitis or alveolar infectious pulmonary disease including toxicity of cytotoxic patients with chemotherapy for hematologic malignancies. Non-

These diseases are characterized by bronchiectasis caused by decreased clear-

Cancer Chemotherapy

Neutropenia is one of the major side effects of cancer chemotherapy, and is associated with an increased incidence of bacterial and fungal infection. Bacterial infections are generally caused by pyogenic or enteric bacteria such as Staphylococcus species, Streptococcus species, and Enterococcus, or gram-negative organisms such as E. coli, Pseudomonas, and Klebsiella. Invasive pulmonary aspergillosis occurs in about 5% of patients with chemotherapy for hematologic malignancies. Non-infectious pulmonary disease including toxicity of cytotoxic chemotherapy agents with resulting pneumonitis or alveolar damage must also be considered.125,126

Intrinsic Disorders of Immunity in Adults

Mucociliary Dysfunction

Disorders of the mucociliary defenses of the airways predispose the host to infections caused by decreased clearance of inhaled infectious agents. Mucus serves to trap respiratory pathogens, which are then cleared by a combination of coughing and ciliated respiratory epithelium, which lines the nasal cavity, sinuses, trachea, bronchi, and bronchioles to the terminal bronchioles.124 The classic disorders of mucociliary dysfunction are cystic fibrosis and Kartagener's. These diseases are characterized by bronchiectasis caused by chronic airways inflammation, which is best assessed using thin section CT. Acquired disorders are occasionally seen, from inhalational injury.

Cystic Fibrosis

Cystic fibrosis is caused by mutation of a transmembrane protein causing dysfunction of chloride transport, as well as dysregulation of other ion channels. Increased viscosity of the mucus layer coating the airways results in ciliary dysfunction and retention of secretions, causing airway inflammation and increasing susceptibility to infection, although other mechanisms for the chronic airway damage have been proposed.125,126 Survival is increasing, and adults with cystic fibrosis are an increasingly large segment of the patient population. Median survival for patients with cystic fibrosis reached 36.8 years in 2005.127 Prevalence of pathogens causing respiratory infection in cystic fibrosis varies with patient age, with Pseudomonas aeruginosa being most common in patients from teens to adulthood, followed by staphylococcal infection. Other common pathogens include H. influenzae, Stenotrophomonas maltophilia, and Burkholderia cepacia complex.128 The Cystic Fibrosis Foundation presently recommends chest radiographs every 2 years as standard of care, with increased frequency as dictated by pulmonary exacerbations. CT, particularly HRCT, is superior in both detecting disease and monitoring severity of complications such as bronchiectasis and consolidation. Findings on CT correlate with pulmonary function tests, and CT can detect findings such as central bronchiectasis that may not manifest as PFT abnormalities (Fig. 15).126,129 Findings on CT may also be predictive of outcome in cystic fibrosis therapy.130 Typical findings in cystic fibrosis in one study of 47 patients who underwent HRCT include, in order of frequency, bronchiectasis (98%), atelectasis/consolidation (81%), bronchial wall thickening (77%), tree-in-bud nodules (74%), and mucus plugging (72%).131

Primary Ciliary Dyskinesia (Kartagener)

Primary ciliary dyskinesia is a rare disorder of ciliary function caused by dynein protein derangement. Abnormal function of dynein in cilia and flagella causes dysmotility in these structures including in the respiratory tract and in spermatozoa. A randomization of body symmetry occurs, so that in half of patients with primary ciliary dyskinesia, there is situs inversus totalis, an entity described in 1962 by Kartagener and Stucki.132 Clinical findings include recurrent upper and lower respiratory tract infections, bronchiectasis, and infertility.133 Radiographic findings resemble cystic fibrosis, with bronchial wall thickening, consolidation, and bronchiectasis, although generally are less severe.134 Although primary ciliary dyskinesia is associated with chronic infection much like cystic fibrosis, pulmonary function declines can be stabilized with aggressive antibiotic treatment and physiotherapy.135,136

Inborn Disorders of Immunity

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) is a genetic immunodeficiency occurring in approximately 1 of 250,000

FIGURE 14. Frontal chest radiograph of a 37-year-old man with longstanding history of AIDS (CD4 count 46/μL) demonstrates dense, calcified nodules caused by previous infection with Varicella pneumonia.
in the United States. The cause of CGD is a defect in nicotinamide adenine dinucleotide phosphate-oxidase in phagocytic cells, preventing intracellular oxidative killing of catalase-positive bacteria and fungi. Although the majority of patients are diagnosed in childhood, some patients are not diagnosed until adulthood. CGD most commonly presents as recurring infections of the skin and lungs. Incidence of pneumonia is 80% in this population. 

Aspergillus is the most common causative agent of pulmonary infection, followed by staphylococcal species, and infection with Aspergillus is the most common cause of death.\textsuperscript{137,138}

Miscellaneous Disorders of Immunity in Adults

Alcoholism

Alcohol abuse is associated with suppression of host immunity and an increased risk of aspiration. An increased incidence of varied infections has been described including community-acquired pneumonias, anaerobic abscess, tuberculosi, and \textit{Legionella pneumophila}. Patients who abuse alcohol have an increased incidence of pneumococcal pneumonia, and mortality from pneumonia is increased relative to nonalcoholic control.\textsuperscript{139,140}

Diabetes

Diabetes mellitus suppresses host immunity through a number of mechanisms including a reduction in granulocyte function. An increase in pulmonary infections is seen, including influenza, mucormycosis, staphylococcal pneumonia, tuberculosis, and gram-negative organisms. Diabetes mellitus is an independent predictor of mortality from pneumonia.\textsuperscript{141,142}

Pattern-Based Approach to Imaging

Ground-Glass Opacity

Ground-glass opacities are areas of increased lung opacity that do not obscure lung interstitium and pulmonary vascularity. If ground-glass opacity is present in isolation in the immune compromised patient, differential diagnosis is relatively compact, and centers on opportunistic infection. Ground-glass opacity in the setting of AIDS and hypoxemia and dry cough is strongly suggestive of \textit{Pneumocystis} pneumonia.\textsuperscript{24,26} Other considerations include CMV pneumonia and HSV pneumonia. CMV pneumonia does not form cysts as in PCP, but the 2 entities may not be otherwise distinguishable on imaging. CMV pneumonia may occur as small ground-glass nodules. In one series, the presence of centrilobular nodules, rare in PCP, helped to differentiate viral pneumonia from PCP.\textsuperscript{26} HSV pneumonia is a rare cause of isolated ground-glass opacities, more commonly causing consolidation and effusion. A clinical history of mucous membrane ulcers is helpful, as these tend to precede pulmonary symptoms.\textsuperscript{143} Respiratory syncytial virus pneumonia is typically associated with ground-glass opacities. \textit{Mycoplasma} pneumonia also presents as ground-glass opacities, although more commonly in immunocompetent patients, and often with a more focal lobular ground-glass pattern with frequent ill-defined centrilobular nodules. Noninfectious causes of ground-glass opacity are occasionally seen, and include edema, hypersensitivity or drug-induced pneumonitis, radiation pneumonitis, pulmonary hemorrhage, and idiopathic interstitial pneumonitis such as respiratory bronchiolitis-interstitial lung disease.\textsuperscript{24,143}

Consolidation

Most causes of consolidation in the setting of immune compromise are from bacterial pneumonia, such as \textit{Staphylococci} and gram-negative pneumonias. Streptococcal pneumonia is reduced in prevalence in the setting of immune compromise likely because of the relative increase in other opportunistic infections.\textsuperscript{39} The most common causes of consolidation in AIDS are bacteria, tuberculosis, atypical myco-
bacteria, and Cryptococcus. Legionella, Nocardia, and Rhodococcus also present with segmental or lobar consolidation, with the latter seen almost exclusively in the setting of AIDS. Tumors such as lymphoma and Kaposi sarcoma as well as primary pulmonary neoplasms are an important cause of consolidation. Infections more commonly associated with ground-glass opacities or nodules can, with progression of disease, result in consolidation, although substantial consolidation is rare in viral infection. 

**Nodules**

Pulmonary nodules are a frequent finding on thoracic CT in patients with immune compromise. Size and distribution of nodules is helpful in narrowing the differential, as is the presence of cavitation. Miliary nodules, typically presenting as numerous nodules 1 to 3 mm in diameter with random distribution, are seen in the setting of tuberculosis and fungal infection. The miliary form of tuberculosis is not associated with lymphadenopathy. Small centrilobular nodules with tree-in-bud distribution suggest airways invasive aspergillus, tuberculosis, and endobronchial spread of bacterial pneumonia.

Larger nonmiliary nodules may be caused by a large number of diseases. In the immunocompromised patient, common causes are fungal infection, viruses, and septic emboli. In one study, a diameter of <10 mm was the only independent predictor of a viral etiology for multiple lung nodules, exclusive of tree-in-bud nodules, although no miliary tuberculosis or fungal infections were noted in the sample. Aspergillus, Candida, and Cryptococcus are common fungal agents. Mucormycosis is indistinguishable from Aspergillus radiographically. Cavitary nodules are seen in nocardiosis, septic emboli, and in angioinvasive aspergillosis.

Primary and metastatic neoplasms such as lymphoma and Kaposi sarcoma may present as nodules. Lymphoma may present without hilar or mediastinal lymphadenopathy in the setting of immune compromise. Irregular or “flame-shaped” nodules are commonly seen in Kaposi sarcoma, as are peribronchovascular nodules. PTLD should be considered in the setting of transplantation.

**Reticulation**

Intralobular and interlobular septal thickening is seen most commonly in the setting of interstitial edema, but it is associated with infections and lymphangitic spread of malignancy. Reticulation can be seen in about 20% to 30% of patients with bacterial, atypical bacterial, fungal, and viral pneumonias, and does not allow differentiation between these etiologies.

**Summary**

The type and severity of immunocompromise can serve as an important guide in approaching radiologic findings in patients with both infectious and noninfectious pulmonary diseases. Refine considerations based on clinical factors such as the use of antiretroviral or prophylactic medications, or time from transplantation. Then, consider patterns of disease at imaging. Although arriving at a specific diagnosis from imaging may be difficult, imaging may provide a useful guide to diagnosis and complements clinical, bronchoscopic, and laboratory investigation.

**REFERENCES**

76. Swigris JJ, Berry GF, Rafaa TA, et al. Lymphoid interstitial pneumo-
77. Das S, Miller RF. Lymphocytic interstitial pneumonitis in HIV infected
78. Ramaswamy G, Jagadhu V, Tchertkoff V. Diffuse alveolar damage and
    interstitial fibrosis in acquired immunodeficiency syndrome patients
    without concurrent pulmonary infection. Arch Pathol Lab Med. 1985;
    pneumonitis in patients with AIDS; radiologic features. AJR Am J
    pneumonitis: a common cause of pulmonary disease in the acquired
    18:136–147.
82. American Thoracic Society/European Respiratory Society International
    Multidisciplinary Consensus Classification of the Idiopathic Interstitial
83. Eaton ME. Selected rare, noninfectious syndromes associated with HIV
    infection. Top HIV Med. 2000;8:212–221.
84. Mehta NJ, Khan IA, Mehta RN, et al. HIV-related pulmonary hyper-
    related to HIV infection: improved hemodynamics and survival asso-
    in human immunodeficiency virus-associated pulmonary arterial hyper-
87. Diaz PT, King MA, Pacht ER, et al. Increased susceptibility to pulmonary
    tional Society for Heart and Lung Transplantation: twenty-third official
89. Speich R, van der Bij W. Epidemiology and management of infections
    Imag. 2002;17:102–112.
    in the adult. Semin Roentgenol. 2006;41:26–35.
    lung transplantation: detection using expiratory HRCT. Chest. 1998;
    340:1081–1091.
94. Soyer P, Devine N, Fraichon I, et al. Computed tomography of compo-
95. Collins J, Muller NL, Kazerooni EA, et al. CT findings of pneumonia
    after lung transplantation: frequency, clinical characteristics, and im-
98. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry.
99. Moskowitz SM, Gibson RL, Effmann EL. Cystic fibrosis lung disease:
    genetic influences, microbial interactions, and radiological assessment.
    Bethesda, MD: Cystic Fibrosis Foundation; 2005.
    marrow transplantation: high resolution CT and pathologic findings.
102. Worthy SA, Flint JD, Muller NL. Pulmonary complications after bone
    cytogram alone on the incidence of CMV viremia in CMV-seropositive
    lung transplantation: detection using expiratory HRCT. Chest. 1998;
105. Reams BD, McAdams HP, Howell DN, et al. Posttransplant lympho-
106. Moskowitz MV, Adams RH. Pulmonary complications in bone marrow
    in marrow transplant recipients: a 20 year experience. Bone Marrow
    2020.
    marrow transplantation: high resolution CT and pathologic findings.
111. Franquet T, Lee KS, Muller NL. Thin-section CT findings in 32
    immunocompromised patients with cysteumovirus pneumonia who do
    in patients after bone marrow transplantation: high resolution CT
114. Gasparetto EL, Ono SE, Escuissato D, et al. Cysteumovirus pneu-
    monia after bone marrow transplantation: high resolution CT findings.
115. Chemaly RF, Ghosh S, Bodey GP, et al. Respiratory viral infections in
    adults with hematologic malignancies and human stem cell transplan-
    tation recipients: a retrospective study at a major cancer center. Med-
116. Joos L, Tamam M. Breakdown of pulmonary host defense in the
117. Franquet T, Muller NL, Gimenez A, et al. Spectrum of pulmonary
    aspergillosis after lung transplant recipients: case series and review of
118. Chae EI, Seo JB, Kim SY, et al. Radiographic and CT findings of thoracic
    complications after pneumonecmy. Radiographics. 2006;26:
    1449–1468.
119. Stannard W, O’Callaghan C. Ciliary function and the role of cilia in
120. Chen MF, Payne D, Pils S, et al. Mucous properties in children with
    primary ciliary dyskinesia: comparison with cystic fibrosis. Chest.
    2004;125:118–123.
    primary ciliary dyskinesia: comparison with cystic fibrosis. Chest.
    2004;125:118–123.
122. Moskowitz SM, Gibson RL, Effmann EL. Cystic fibrosis lung disease:
    genetic influences, microbial interactions, and radiological assessment.
    Bethesda, MD: Cystic Fibrosis Foundation; 2005.
124. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry.
125. Robinson TE. High-resolution CT scanning: potential outcome mea-