Chapter

86

AIDS and the Lung

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INTRODUCTION

Patients with HIV infection can develop respiratory dysfunction due to a wide range of infectious, neoplastic, embolic, toxic and cardiovascular disorders (Table 1). Physicians must recognize that these patients may have pulmonary presentations totally unrelated to their HIV infection. Moreover, infectious pulmonary involvement in HIV may be due to community-acquired pathogens and not necessarily due to opportunistic organisms. In addition, risk factors for HIV infection, such as IV drug abuse may also contribute to pulmonary disease like endocarditis with septic pulmonary emboli, aspiration pneumonia due to altered mentation or talc granulomatosis.

The pulmonary complications of HIV infection Study (PCHIS) conducted in the pre-HAART era concluded that HIV patients more often had URTI and acute bronchitis than bacterial pneumonias or PCP, although the latter were commoner causes of hospitalization. Worldwide, and in India, tuberculosis is a leading cause of death in this cohort, and in endemic areas, *Histoplasma capsulatum* and *Coccidioides imitis* are among the most frequent infections seen.

Symptoms and Signs

The multiplicity of respiratory pathogens and the atypical presentations encountered in the face of HIV mandates a thorough history and clinical examination as a pre-requisite for the diagnosis and management of these diseases. While the approach to these clinical clues is detailed in Table 2, it is pertinent to underline a few caveats. All of the HIV-associated respiratory diseases may present with cough, dyspnea, and less frequently pleuritic chest pain. Bacterial pneumonias have been seen to co-exist with PCP, and both are common in their

Table 1: Pulmonary diseases seen more often in HIV infected patients

Opportunistic infections

Bacterial
- Streptococcus pneumoniae
- Haemophilus influenzae
- Staphylococcus aureus
- Pseudomonas aeruginosa
- Klebsiella pneumoniae
- Rhodococcus equi
- Mycobacterium tuberculosis
- Atypical mycobacteria

Fungal
- Pneumocystis jiroveci (previously P. carinii)
- Cryptococcus neoformans
- Histoplasma capsulatum
- Coccidiodes imitis
- Penicillium marneffi

Viral
- CMV
- EBV
- HSV
- VZV

Protozoal
- Toxoplasma gondii
- Strongyloides stercoralis

Neoplasms
- Lymphoma
- Kaposi sarcoma
- Mantle cell lymphoma
- Squamous cell carcinoma (?)

Other disorders
- Asthma
- Pulmonary hypertension
- Cardiomyopathy/congestive cardiac failure
- Premature atherosclerosis
- Immune reconstitution inflammatory syndrome (IRIS)
- Alveolar hemorrhage

Table 2: Clinical clues to respiratory diseases in HIV

Clinical setting
Ambulatory / OPD patient: URTI > acute bronchitis > bacterial pneumonia / PCP
In patient: Bacterial pneumonia > PCP > TB > Pulmonary Kaposi / Cryptococcus pneumonia
ICU: PCP > Bacterial pneumonia
Geographic location
Mycobacterium TB
Endemic fungi (Histoplasma capsulatum / Coccidioides imitis)
HIV transmission category
MSM: Increased incidence of Kaposi sarcoma
IDU: Increased risk of bacterial pneumonia, TB, and IDU related pulmonary complications
Habits
Cigarette smoking: Increased incidence of bacterial bronchitis/ pneumonia, COPD, bronchogenic carcinoma
Travel and residence
Assess for TB, endemic fungal diseases
Medical background
Increased incidence of recurrence of bacterial pneumonia, PCP, fungal pneumonias
Prophylaxis decreases risk of PCP, Toxoplasma
Signs and symptoms
Respiratory symptoms and symptom duration
Symptoms/signs suggesting extrapulmonary/ disseminated disease
Chest findings: Focal/non-focal

own rights. A differentiation between these two is often challenging and this has been elucidated in Table 3. Invasive pulmonary mycoses are major entities in HIV medicine, and the geographic location and the patient's occupation, are both important. Penicilliosis, caused by a dimorphic fungus, Penicillium marneffei, is a febrile wasting disease, that mimicks other granulomatous diseases like tuberculosis or histoplasmosis, and has become the major endemic fungus of South East Asia, and presents with skin, lung and other visceral lesions.

Sinusitis is more common in HIV-infected persons. As the CD4 declines, the frequency increases, although the clinical presentation and the management issues are identical to that in the immuno-competent population. Similarly, bronchitis is more common in HIV and increases in frequency with disease progression. However, recurrence leads to anatomical damage and bronchiectasis. HIV-infected persons with recurrent bronchitis or bronchiectasis who are smokers, should be strongly encouraged to quit smoking.

Pulmonary Kaposi sarcoma characteristically presents with a nonproductive cough, dyspnea, and occasionally fever. The diagnosis is usually established by bronchoscopy, and transbronchial biopsies are advocated if no endobronchial lesions are seen. The incidence of pulmonary Kaposi sarcoma is decreasing, while that of pulmonary NHL in HIV patients is increasing.

Table 3: Differential presentations of bacterial pneumonia and PCP

Parameter	*Bacterial pneumonia*	*Pneumocystis carinii pneumonia*
CD4 count	Any	< 200 cells / µL
Symptoms	Fever, chills, rigor	Fever
	Dyspnea less	Dyspnea more
	Pleuritic chest pain	
	Productive cough	Non-productive cough
	Purulent sputum	No sputum
Symptom duration	Typically 3–4 days	Typically 2-4 weeks
Lung signs	Focal findings	Often unremarkable, inspiratory crackles
Lab tests	Leucocytosis, LDH varies	WBC count varies LDH frequently elevated
CXR	Patchy, focal > multifocal	Diffuse > focal
	Unilateral, Consolidation	Bilateral, Reticular
Cysts	Rarely	15–20%
Pleural effusions	25–50%	Very rarely
Adenopathy	Rarely	Very rarely
Pneumothorax	Rarely	Occasionally
Normal CXR	Never	Occasionally

HIV-associated pulmonary disease is occasionally attributable to one of the two interstitial pneumonitides: lymphocytic interstitial pneumonitis (LIP) and non-specific interstitial pneumonitis (NIP). Symptoms of LIP include dyspnea, nonproductive cough and fever. Lung examination may be unremarkable or reveal inspiratory crackles. Additional findings include clubbing, lymphadenopathy, salivary gland enlargement or hepatosplenomegaly. The CXR characteristically shows bilateral reticulonodular infiltrates with lower lung predominance. The diagnosis requires histological confirmation following biopsy.

The symptoms, signs and CXR findings of NIP are indistinguishable from LIP, as well as from PCP. However, at CD4 counts < 200 / µL PCP is common while NIP is not. The diagnosis of NIP requires histologic confirmation and exclusion of other etiologies.

Knowledge of extra-pulmonary disease can be occasionally utilized to infer a respiratory etiology without investigative documentation. Lymphadenopathy or hepatosplenomegaly usually indicates either mycobacterial or fungal disease or Non-Hodgkin's lymphoma. A patient with pneumonia, CD4 count < 200/µL and altered mental state may have a common etiology of *Cryptococcus neoformans* whereas another with focal neurological presentations (in place of altered mentation) is likely to have *Toxoplasma encephalitis* with pneumonitis. New cutaneous lesions may suggest disseminated fungal disease. Although mucocutaneous Kaposi sarcoma suggests pulmonary involvement with the same etiology, workers have found that 15% of bronchoscopy proved Kaposi cases had no evidence of mucocutaneous Kaposi lesions.

Table 4: Usual CD4 lymphocyte counts for common respiratory diseases in HIV

Any CD4 count
Upper respiratory tract infection
Acute bronchitis/sinusitis
Bacterial pneumonia (most common Strep. pneumoniae, Haemophilus spp.)
Mycobacterium tuberculosis pneumonia
Non-Hodgkin's lymphoma
Bronchogenic carcinoma
Nonspecific interstitial pneumonitis
CD4 count < 200 / µL
Pneumocystis carinii pneumonia
Cryptococcus neoformans pneumonia
Bacterial pneumonia
Extra-pulmonary/disseminated pneumonia
CD4 count < 100 / µL
Pseudomonas pneumonia
Toxoplasma gondii pneumonia
Pulmonary Kaposi sarcoma
CD4 count < 50 / µL
Histoplasma capsulatum usually associated with disseminated disease
Coccidioides imitis usually associated with disseminated disease
Aspergillus pneumonia
CMV pneumonia usually associated with disseminated disease
Mycobacterium avium complex usually associated with disseminated disease

Laboratory Tests

The CD4 count remains an excellent indicator of an HIV positive person developing a specific infection of neoplasm. This has been elucidated in Table 4. It must be mentioned, however, that the CD4 count should serve as a guide as to whom pulmonary diseases are more common in that population. Exceptions to such guidelines occurred before the HAART era, and continue to occur today. ABG analysis is indicated for persons with moderate to severe pulmonary dysfunction. ABG analysis is useful for prognosis and for making clinical decisions regarding whether and where to admit the patient and whether corticosteroids are indicated in patients with PCP. The total leucocyte count rises in HIV patients as well, although the rise may be relative to the patients' baseline value. Pancytopenia suggests an infectious or neoplastic process in the bone marrow. Elevated serum LDH is a sensitive but non-specific marker of PCP. Patients with PCP and an initially raised or a rising serum LDH despite PCP therapy have a poor prognosis, in contrast to patients responding well to PCP therapy, who usually have a decline in serum LDH levels over time.

Imaging

The characteristic chest radiographic findings for selected HIV associated pulmonary diseases are presented in Table 5. However, inter-observer variations and the paucity of standardized interpretative approaches, limits the use of this accessible and affordable tool for reaching an etiological diagnosis of pulmonary affection in HIV.

HRCT chest is extremely useful in cases of suspected PCP with normal chest X-rays that occur in 20-40% of cases. Although the presence of ground glass opacities

Table 5: Predominant chest radiographic patterns for selected pulmonary diseases in HIV

Pulmonary disease	*Pattern of involvement in chest X-ray*
Bacterial pneumonia	Lobar/alveolar
PCP	Bilateral, interstitial or mixed
M tuberculosis CD4 < 200 / µL	Non-cavitary, military, adenopathy
M tuberculosis CD4 200 - 400 / µL	Cavitary
M tuberculosis CD4 > 400 / µL	Cavitary
C neoformans pneumonia	Interstitial
CMV pneumonia	Interstitial or reticulo-granular
Kaposi sarcoma	Nodules
NHL	Nodules or masses

(GGO) in non-specific, its absence strongly rules out PCP. A predominance of nodules smaller than 1cm in diameter in a centrilobular distribution suggests the presence of an opportunistic infection (OI), whereas nodules larger than 1 cm points towards a possible neoplasm.

Gallium 67 scans has limited role in HIV infection. When a positive test is defined as any gallium uptake (1+) over the lung parenchyma, this test has poor specificity (50%) for PCP. However, using more stringent criteria, where a positive test is defined as uptake equal to (3+) or greater than (4+) that of the liver, the specificity increases to 80%. Much more important is the fact that in contrast to OIs, NHL, and non-specific interstitial pneumonia (NSIP), Kaposi sarcoma is gallium negative. This helps to prove the diagnosis in a HIV patient with pulmonary involvement and mucocutaneous Kaposi lesions, as also to incriminate Kaposi, when a patient with known pulmonary Kaposi sarcoma presents with worsening respiratory symptoms and has a negative gallium scan to rule out a superimposed OI.

It is pertinent to mention here that pulmonary function tests are non-specific in HIV medicine, with PCP showing decreased lung volumes and decreased diffusing capacity to carbon monoxide.

Table 6: Therapeutic strategies for common pulmonary diseases in HIV

Disease	*Preferred treatment regimen*	*Second therapeutic option*
PCP	Trimethoprim 15-20 mg/kg/d + sulfamethoxazole 75-100 mg/kg/d, 21 days, in 3 or 4 divided doses.	Trimethoprim 15 mg/kg/d + dapsone 100 mg/d, 21 days
	Add Prednisolone 40 mg for 5 days, 20 mg for 5 days, 10 mg for 11 days if PO_2 < 70 mm Hg	Add Prednisolone 40 mg for 5 days, 20 mg for 5 days, 10 mg for 11 days if PO_2 < 70 mmHg
Pulmonary aspergilosis	Voriconazole 6 mg/kg IV BD for 1 week, then 200 mg BD	Amphotericin B 1.0-1.4 mg/kg/day
Pulmonary cryptococcosis	Fluconazole 200 mg/day indefinitely, or till immune reconstitution	Itraconazole 200 mg BD
Pulmonary histoplasmosis	Initial: Amphotericin B 0.5-1.0 mg/kg/day IV, for 7-10 days Maintenance: Itraconazole 200 mg BD	Fluconazole 1600 mg on 1st day, then 800 mg / day for 12 weeks, then 400 mg daily
Coccidioidomycosis	Initial: Amphotericin B 0.5 mg/kg/day IV, for 8 weeks Maintenance: Fluconazole 400 mg/d	Initial: Fluconazole 1600-3200 mg/d for 8 weeks Maintenance: Amphotericin B 1 mg/kg/week IV
Penicillium marneffei pneumonitis	Itraconazole 400 mg/d for 2 weeks, then 200 mg/d till immune reconstituion	Amphotericin B 0.7 – 1.0 mg/kg/day IV for 2 weeks followed by Itraconazole
CMV pneumonia	HAART + Ganciclovir 5 mg/kg IV BD for 2-3 weeks + Foscarnet 60 mg/kg 8 hrly or 90 mg/kg 12 hrly for 3 weeks.	HAART + Foscarnet 60 mg/kg 8 hrly or 90 mg/kg 12 hrly for 3 weeks
Nocardia asteroides pneumonia	TMP – SMX 5-15 mg/kg/d (TMP) for 6 months	Minocycline 100 mg BD for 6 months
Rhodococcus equi	Vancomycin 2 g/d IV + Rifampin 600 mg QID for 2-4 weeks, followed by Ciprofloxacin 750 mg BD long term	Erythromycin 2-4 g/day IV
Lymphoid interstitial pneumonitis/non-specific interstitial pneumonitis	HAART Steroid use is debatable, but often used for progressive disease despite HAART.	

Approach to Therapy

The principles of treatment of patients with community-acquired pneumonia are same in HIV patients as in the immuno-competent population. The decision to admit a HIV patient with community acquired pneumonia should be based upon the presence of one or more of these factors: CD4 count < 100/µL, septic shock, cavities on CXR, multilobar infiltrates, and pleural effusion. PCP usually responds within 5–8 days. Failure of PCP to respond to standard TMP-SMX therapy should raise the suspicion of another diagnosis. Bronchoscopy is the procedure of choice for PCP as it provides the maximum diagnostic yield. A patient may have concurrent etiologies such as non-cardiogenic edema and a trial of diuresis maybe warranted. Although not established as clinically significant, specific point mutations in the P. carinii dihydropteroate synthase gene – the enzymatic target of sulfmethoxazole and dapsone – are associated with an increased risk of TMP-SMX treatment failure in PCP. The treatment protocols for the common pulmonary disorders encountered in HIV are summarized in Table 6.

The use of potent combinations of antiretrovirals has in some cases exacerbated the underlying OIs transiently, and this has been termed the immune reconstitution syndrome. The worsening of clinical findings and CXR features following initiation of anti – tuberculous therapy has been documented in the past. HIV-infected patients who receive concurrent ATD and HAART are at increased risk of developing such paradoxical worsening. The major features of these immune reconstitution syndromes are hectic fevers, indurated tender lymphadenopathy and worsening cough and breathlessness. Occasionally, meningitis due to OIs may be the manifestation. Those with severe paradoxical symptoms require corticosteroids for symptomatic management, but the treatment of the OI or HAART should not be discontinued.

Prevention of Pulmonary Disease in HIV

On the preventive front, PCP prophylaxis should be initiated both for those completing PCP therapy or those with CD4 counts < 200/ µL, and stopped when CD4 count has remained above 200/µL for more than 3 months. The preferred regime for this prophylaxis is one TMP – SMX DS tablet daily. This same tablet offers protection against *Toxoplasma gondii* pneumonitis and should be initiated at CD4 < 100 / µL, with positive IgG serology and stopped when the count has remained above 200 /µL for more than 3 months (6 months for secondary prophylaxis). Exposure to chickenpox or zoster and no history of chickenpox or negative varicella zoster virus (VZV) antibody mandates varicella zoster immune globulin (VZIG) 625 units (5 vials) within 96 hours of exposure. All HIV patients are candidates for influenza vaccination, and those with CD4 < 200/µL should be strongly recommended to take the pneumococcal vaccine as well. Histoplasmosis prophylaxis is recommended for those with CD4 < 100/µL, in endemic areas, especially if at high occupational risk.

SUGGESTED READING

1. Bartlett JG. Management of complications. In Bartlett JG (Ed). The Johns Hopkins Hospital Guide to Medical Care of Patients with HIV infection; Philadelphia, Lippincott, Williams and Wilkins; 12th edition, 2005;143-92.
2. Huang L. Respiratory disease. In Dolin R, Masur H, Saag MS (Eds). AIDS Therapy, New York, Churchill Livingstone, 2nd edition, 2003;827-52.