PNEUMOLOGY/HIV

Respiratory Pathogens in Bronchoalveolar Lavage in a Puerto Rican Population Infected with the Human Immunodeficiency Virus

YOHANA DE JESÚS-BERRÍOS, MD*; SHEILA GONZÁLEZ, MD*; MARÍA SANTÉ, MD†

Objective. **To describe the respiratory pathogens found in the bronchoalveolar lavage of a Puerto Rican population infected with the human immunodeficiency virus (HIV).**

Background. **Empirical treatment is an accepted strategy for management of HIV-related pneumonia, but it is usually recommended for countries that have knowledge of the prevalent organisms in their population. In Puerto Rico, we have relied on data from the United States, but ethnic and geographical differences have been reported.**

Design. **Case series of a HIV-infected population admitted to an academic hospital in Puerto Rico because of respiratory symptoms and who underwent diagnostic standard bronchoalveolar lavage.**

Results. **From August 1998 to March 2000, 32 bronchoalveolar lavages (BAL) were performed in 31 Puerto Rican HIV patients. Nine (31%) were female. Mean age was 37 years old. Predominant mode of infection of the virus was intravenous drug use in men and heterosexual contact in women. BAL was diagnostic in 17/32 (53%) of the cases. Identified respiratory pathogens were *Pneumocystis carinii* (5), *Mycobacterium tuberculosis* (4), *Staphylococcus aureus* (2), *Pseudomonas aeuruginosa* (1), *Bordetella bronchiseptica* (1), viridans streptococcus (1), *Histoplasma capsulatum* (1), *Cytomegalovirus* (1), and, *Mycobacterium kansassi* (1). Retrospective review of medical records of non bronchoscoped patients for the period added six culture confirmed tuberculosis cases increasing tuberculosis rate to 18% (10/56).**

Conclusions. **Tuberculosis appears to be a more frequent pathogen in Puerto Rico than is reported in the United States. A larger study is needed to confirm this finding and thus to clarify whether an initial presumption of tuberculosis should be assumed in the Puerto Rican HIV population.**

Key words: HIV, Puerto Rican, Respiratory pathogens, Tuberculosis, Bordetella bronchiseptica, Viridans streptococcus

In June 2001, the cumulative total of acquired immunodeficiency syndrome (AIDS) cases in the United States (USA) and its territories reported to the Center for Disease Control was 793,026 (1). For the same period 25,459 AIDS persons were reported in Puerto Rico, and the annual rate per 100,000 populations was 37.0 occupying the second position in the USA and its territories, preceded only by the District of Columbia. At the end of 2003, estimated rate of adults and adolescent living with AIDS in Puerto Rico was 316.6 per 100,000 population compared to 167.3 in the United States (2).

Pulmonary infections remain as a major problem in AIDS patients contributing to significant morbidity and mortality. Even in the era of prophylaxis, *Pneumocystis carinii* pneumonia (PCP) continues to be the most common AIDS-defining diagnosis in the United States and other industrialized countries (3). Nevertheless in the developing countries, tuberculosis is the leading opportunistic infection accounting for up to 44% of AIDS patients (4).

Empirical treatment is an accepted strategy for management of HIV-related pneumonia (5-6), but it is usually recommended for countries that have identified the prevalent organisms (7). In Puerto Rico, we have relied on data from the United States, but as ethnic and geographical differences have been reported (8-10), we conduct this study in order to help in determining if the same principle applies in Puerto Rico.

Objective

To describe the respiratory pathogens found in the bronchoalveolar lavage (BAL) of a Puerto Rican HIV/AIDS population admitted with respiratory symptoms or

*From the Pulmonary Section and †Pathology Department, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico.

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Address correspondence to: Yohana De Jesús-Berrios, MD, Pulmonary Section, School of Medicine, University of Puerto Rico, Medical Sciences Campus, PO Box 365067, San Juan, Puerto Rico 00936-5067. Phone 787-754-0101, ext 3750, email: Ydejesus@rcm.upr.edu

abnormal chest radiograph to an academic hospital from July 1998 to March 2000.

Design. Descriptive study of a series of HIV-infected cases patients 21 years old or older admitted to the University Hospital from August 1998 to March 2000 because of respiratory symptoms, abnormal chest radiograph or unexplained fever who consented for bronchoscopy (FOB) and bronchoalveolar lavage (BAL). If the patient was judged too ill for FOB, non bronchoscopic BAL was performed instead, and samples were managed the same as for FOB.

Bronchoscopy procedure. Bronchoalveolar lavage was performed in a standard manner as previously described (11). Briefly, flexible fiberoptic bronchoscope was advanced to the trachea, bronchial tree was examined and instrument was wedged in a subsegmental bronchus of the right middle lobe in patients with diffuse pulmonary infiltrates or in the affected segment in localized disease. Four 60cc aliquots of 0.9 saline solutions were instilled and the fluid was recovered by gentle aspiration. Lavage fluid was pooled and measured.

BAL analysis. A portion was separated for semi quantitative bacterial culture, and mycobacterium and fungi cultures. The remaining fluid was transported on ice to the Pathology Laboratory at the Puerto Rico Medical Center for cytological examination.

Following standard preserving and staining procedures, one slide was air dried and stained with Diff-Quick-R and three alcohol fixed slides were stained with Papanicolau, GMS silver stain, and acid fast bacilli stain (12). A certified pathologist examined the slides to identify organisms.

Diagnosis of PCP required microbiological demonstration of *P. carinii* in BAL fluid. Cytomegalovirus infection required identification of the characteristic intranuclear or intracytoplasmic inclusion bodies on cytological examination of pulmonary epithelial cells in the lavage fluid (13). *Histoplasma capsulatum* was considered to be the etiologic agent if detected by smears or cultures of BAL fluid. The presence of 10^4 or more colony-forming units/ml of BAL fluid identifies with reasonable accuracy the organism causing bacterial pneumonia (14). Tuberculosis infection required demonstration of *Mycobacterium tuberculosis* isolated on culture.

Statistical Analysis

Descriptive analysis of the data was performed using Epi-Info. Proportion of cases with respiratory pathogens, predominant mode of transmission, gender differences, and clinical characteristics of this group of the Puerto Rican HIV/AIDS patients was analyzed.

Results

Table 1 illustrates the characteristics of 56 HIV patients admitted to an academic hospital in Puerto Rico from August 1998 to March 2000 with respiratory symptoms. Thirty-one patients underwent 32 bronchoalveolar lavages for diagnosis and constitute the BAL population. Twenty-one patients identified in a retrospective record review were not consulted to the Pulmonary service, either because empirical treatment was offered or because diagnosis was established by other method; three patients refused the procedure, and one was considered too ill for the procedure. They constitute the no BAL population.

Table 1: Characteristic of 54 HIV patients admitted with respiratory complaints during the study period.

	BAL population n 31	No Bronchoscopy n 25
Sex Female/ Male	9/22	2/23
Age mean (range)	37 (31-52)	36 (24-55)
Transmission category*		
Male sex male	3	0
Intravenous drug use	16	23
Heterosexual	14	2
Blood transfusion	1	1
Unknown	1	2
Antiviral use	14	8
PCP prophylaxis	8	4
Tuberculin skin test		
Positive	10	4
Negative	3	7
Unknown	18	14
	n=21	n=17
Mean CD4 cells/ml (range)	87(19-511)	126(19-577)
Patients with CD4 less than 50 cells/ml	13	9
Mean viral load copies/ml(range)	172,161 (400-500,000)	186,177 (399-500,000)

BAL: bronchoalveolar lavage; PCP: *Pneumocystis carinii* pneumonia
* may be in more than one category

In the BAL population, nine (29%) were female; mean age was 37 years old. Mode of transmission was intravenous drug use (IDU) in 14, heterosexual partner with HIV in 10, homosexuality in 3, both heterosexual and IDU in two, heterosexual and blood transfusion in one, and unknown in another. Heterosexual contact was the predominant mode of transmission in women (5/9) and IDU in males (13/22). Fifteen patients (48%) were in antiretroviral therapy and 8 in PCP prophylaxis. Tuberculin PPD (purified protein derivative) status was available for 13 and 10 were positive. CD4 lymphocyte count was less than 200 cells $x10^6$/L in 19 of 22 patients having a test result (86%).

BAL was diagnostic in 17/32 (53%) of the cases performed. Table 2 presents the clinical characteristics of the patients in which a respiratory pathogen was identified. Identified organisms were *Pneumocystis carinii* (5), *Mycobacterium tuberculosis* (4), *Staphylococcus aureus* (2), *Pseudomonas aeuruginosa* (1), *Bordetella bronchiseptica* (1), α hemolytic streptococcus (1), *Histoplasma capsulatum* (1), *Cytomegalovirus* (1), and, *Mycobacterium kansassi* (1).

Bacterial pneumonia accounted for 16% of the cases. One of the patients with *S aureus* was an intravenous drug user. The patient showing *Bordetella bronchiseptica* in BALwas a 35 y/o female living with HIV for 12 years, viral load of 500,000 copies/ml, CD4 T less than 20 cells per cmm, and she was not using antiviral therapy or PCP prophylaxis. She complained of fever, cough, and shortness of breath for two weeks, and not quantified weight loss. Chest radiograph showed bilateral interstitial infiltrates and her alveolo-arterial gradient was 610. Non-bronchoscopic lavage showed 100,000 colonies of *Bordetella bronchiseptica*. Initially, she improved on levofloxacin, septra and amikin but finally she died of disseminated *Mycobacterium avium* infection.

The patient showing α hemolytic streptococcus was a 32 years old male intravenous drug user, diagnosed with HIV for 10 years. He had high fever (Temperature 39° C), cough, shortness of breath, and right perihilar infiltrate in chest radiograph. White blood cell count was 1,400 (64% neutrophils, 29% lymphocytes), Hemoglobin 8.4 g, and CD4 40 cells/mm3. BAL showed over 100,000 colonies/ml of pure growth of α streptococcus. Patient was treated with Nafcillin, Biaxin, Septra, and Amikin with good clinical response.

The five patients with PCP were male, none was in PCP prophylaxis, and CD4 was less than 50 in 4/4 patients tested.

Tuberculosis infection accounted for 12.5% of the BAL population. Mode of transmission in this group was: heterosexual contact with a HIV partner in two, and IDU in two. Tuberculin skin test was positive in two and unknown in two. Two patients showed diffuse infiltrates and two patients have localized infiltrates associated to either right paratracheal or hilar adenopathy.

The 25 records of non-bronchoscoped AIDS patients admitted with respiratory complaints during the study period were retrospectively reviewed and 6 demonstrated culture confirmed tuberculosis: four in sputum, one in axillary node biopsy, and one in pleural fluid. Chest radiograph of the one with tuberculous lymphadenitis suggested an upper lobe cavitary lesion, and the one with pleural effusion developed a miliary pattern six months later. The ten cases were male, five were living in jail at the time of admission, seven were intravenous drug users, and seven had CD4 below 200.

Table 2. Clinical characteristics of patients with respiratory pathogens identified in bronchoalveolar lavage

Diagnosis	Case	Sex	Age	Transmission Category	Years living with HIV	Viral Load x10³ copies/ml	CD4 cells per ml	On admission Antiviral	On admission Prevent PCP	PPD Skin test*	Chest radiograph
Pneumocystis	1	M	43	IDU	0	9,200	<20	No	No	U	Diffuse
carinii	2	M	33	MSM	10	150,000	38	No	No	P	Diffuse
	3	M	36	IDU	4	120,000	<20	Yes	No	N	Localized
	4	M	35	Unknown	0	200,000	37	No	No	P	Diffuse
	5	M	35	Heterosexual	12	200,000	N/A	No	No	U	Localized
S aureus	6	F	32	Heterosexual	13	N/a	N/A	No	No	U	Localized
	7	M	39	IDU	13	300,000	268	No	No	U	Diffuse
B bronchiseptica	8	F	35	IDU	12	500,000	<20	No	No	U	Diffuse
P aeuruginosa	9	M	38	IDU	8	340,000	<20	Yes	No	U	Localized
A Streptococcus	10	M	32	IDU	10	N/A	40	Yes	No	P	Localized
M tuberculosis	11	M	31	Heterosexual	N/A	270,000	72	Yes	Yes	P*	Diffuse
	12	M	37	Heterosexual	0.4	2,100	57	Yes	No	U	Localized, Adenophaties
	13	M	37	IDU	5	1,500	130	Yes	No	P*	Diffuse
	14	M	40	IDU	15	N/A	N/A	No	No	U	Localized, Adenophaties
H capsulatum	15	M	33	IDU	1	86,000	<20	No	No	U	Diffuse
Cytomegalovirus	16	M	38	MSM	8	8,200	<20	Yes	Yes	N	Diffuse
M kansasii	17	M	37	Heterosexual	2	300,000	<20	No	Yes	N	Diffuse

F: female; IDU: intravenous drug user; M: male; MSM: male sex male; N:negative; N/A:not available; P:positive; PCP: *Pneumocystis carinii* pneumonia; U: unknown; *PPD was recorded as positive by history, but it was not repeated on this admission.

Table 3. Non bronchoscoped patients with culture confirmed tuberculosis

Case	*Age (years old)*	*Sex*	*Transmission Category*	*Tuberculin skin Test*	*Chest x ray*	*CD4*	*Source of culture confirmed tuberculosis*	*Other*
1	32	M	IDU	Negative	Left upper lobe Cavity, Adenopathy	<20	Sputum and FNA of cervical adenopathy	Cervical adenopathies
2	38	M		Unknown	Left perihilar	30	Sputum	
3	39	M	IDU	Unknown	Not available	26	Sputum	
4	30	M	IDU Unknown, Promiscuity	Positive on 1992 Negative on 1999	Ill defined Lung cavity	268	Axillary node biopsy	Cervical and axillary adenopathies
5	46	M	IDU	Positive	Bilateral apical Infiltrates	577	Sputum	
6	31	M	IDU	Positive	Pleural effusion	57	Pleural	Hepatomegaly, Spenomegaly, adenopathies

Discussion

Pulmonary disease is a major contributor to morbidity and mortality in patients with HIV infection. Combination antiretroviral therapy with protease inhibitors has been a major contributor to a recent decline in HIV-related opportunistic infection (15). In the industrialized countries, *Pneumocystic carinii* remains as the most common opportunistic respiratory pathogen isolated from BAL even in the current era of PCP prophylaxis, while *Mycobacterium tuberculosis* is identified in less than 5% of the cases with respiratory illness (3,16-17). In the developing countries protease inhibitors containing antiretroviral therapy are seldom used and tuberculosis remains the most common life threatening HIV related infection (18).

In Puerto Rico, during two decades of the HIV epidemic, physicians have relied on US data for empirical treatment of the HIV population. PCP was the most common reported disease category in Puerto Rico accounting for 27% of the cases in 1997, but only 20% of the reported cases of PCP were confirmed (19).

The respiratory pathogens identified in BAL in a hospitalized Puerto Rican AIDS population are described. In this series, bacterial pneumonia was the most frequent respiratory infection, as previously described in the HIV population (3). Nevertheless, *Streptococcus pneumonia* was not identified, probably because it is a fastidious organism to culture and because empirical treatment is routinely institute before bronchoscopy. Two findings deserve discussion: *Bordetella bronchiseptica* was identified in a 35 y/o female in advanced stage of HIV, and α hemolytic streptococcus arises as the probable pathogen in a severely immunosuppressed AIDS patient.

B bronchiseptica is a pleomorphic gram-negative coccobacillus that causes respiratory tract infections in animals such as dogs, cats, horses, and rabbits, but it is rarely reported as cause of human infection. It is almost always associated to severe underlying illness and several cases have been reported in HIV infected patients (20). Dworkin analysis of data from the Adult and Adolescent Spectrum of HIV Disease surveillance project describes nine patients with *B. bronchiseptica* infection among 41,336 patients enrolled in the project. The series includes patients with a range of severity of lower respiratory tract infection as well as disseminated infection; six patients had pneumonia. The patients usually have low CD4 cell count, and interstitial infiltrates were common. His work suggests that *Bordetella bronchiseptica* may be under diagnosed when specimens for culture are not obtained. Our patient was severely ill in the late stage of HIV. To our knowledge this is the first case of *B. bronchiseptica* reported in PR.

Alpha streptococcus is usually not considered a respiratory pathogen. It is a normal flora of the human oral cavity and its presence in sputum culture is not reported. Nevertheless, it is known that neutropenic patients with cancer may have normal flora bacteria as significant pathogens (21). Streptococcus viridans causing pneumonia has been described in children, cancer patients and even in healthy adults (22). Percutaneous transtracheal aspirate has been used for diagnosis when a pure culture is recovered (23).

It has been suggested that BAL culture showing 10^3 colonies colony forming unit (cfu)/ml as the threshold value for a positive culture for any bacterial species not considered normal flora. As the criterion for a positive

culture is varied from 10^3 to 10^5 cfu/ml of a bacterial pathogen, the sensitivity falls with a concomitant rise in specificity (24).

The patient reported in this study was severely immunosupressed, as evidenced by a CD4 below 50 cells/mm^3, and profound neutropenia. Although other unidentified bacteria could be responsible for the pneumonia, the presence of 100,000 cfu/ml of pure growth in BAL suggests alpha hemolytic streptococcus as the probable etiology. We alert that viridans streptococcal pulmonary infections may be overlooked in the HIV population because these organisms usually respond to the antibiotics commonly prescribed for pneumonia, and laboratories ignore the organism as normal flora. BAL with colonies count may be helpful identifying the organism, which may be particular important in the HIV population susceptible to penicillin resistant species.

PCP was the most common opportunistic respiratory pathogen identified in BAL. None of the five patients were in PCP prophylaxis in spite of CD4 less than 50 in 4/4 patients, suggesting poor access to adequate health care.

Tuberculosis cases confirmed by BAL fluid culture were higher than expected (12.5%). To evaluate a selection bias, we retrospectively review medical records of non bronchoscoped patients in the institution during the study period. This added six culture confirmed cases increasing tuberculosis rate to 18% (10/56). This is higher than reported in the USA and it is of concern because HIV patients with respiratory complaints are not routinely evaluated for mycobacterium infection. Fifty seven % (32/56) of the study population was not skin tested for tuberculosis. CD4 was less than 200 cells/mm3 in seven of nine (78%) of the tuberculous population tested, but mean CD4 was low for the complete sample.

The incidence of HIV-associated tuberculosis has been increasing worldwide, especially in developing countries (25). Myoung-don Oh found tuberculosis as the single most important HIV-related infection in South Korean patients accounting for 25% of the 173 HIV-infected patients in a referral hospital (26). Sixty-two percent of the 173 patients were HIV-infected by heterosexual contacts. Fang reported a large proportion of tuberculosis cases in HIV-infected patients in Taiwan, and most were immigrants from Southeast Asia (27). High prevalence of tuberculosis was considered the most probable explanation for its frequency in their HIV/AIDS population. Lado Lado analyses the clinical characteristic of 92 cases of tuberculosis in seropositive HIV patients in Spain. Most of them (81.5%) were intravenous drug users (28).

In this study, seventy percent (39/56) reported IDU as the likeliest mode of HIV transmission and six of ten tuberculosis cases were in jail at the time of admission. Tuberculosis is more common among prisoners because high prevalence of risk factors for tuberculosis and because crowded and poorly ventilated conditions may promote spread of tuberculosis and other respiratory diseases (29). Either jail imprisonment or marginal situations associated to IDU may explain high tuberculosis rate in this series.

Puerto Rican AIDS population is different to the USA. Sixty two percent of the USA HIV/AIDS patients report homosexual contact as likeliest mode of transmission (30). In PR 21.5% of male report the same, while 64.4% report IDU (31). The general socio-demographic profile of 1520 adults or adolescents 18 years or older with AIDS or HIV infection enrolled in the Human Retrovirus Registry at the time they present to the University Hospital Ramón Ruiz Arnau and the Bayamón Immunology Clinic revealed 70% to be unemployed, and forty-seven percent (47%) of the subjects had a clinical or immunological criterion to be considered as an AIDS case at first presentation (32). These facts point to marginal social conditions of the Puerto Rican HIV/AIDS population, and late access to health care services.

Summary

A HIV infected population of 54 patients with respiratory symptoms admitted to an academic hospital in San Juan, Puerto Rico from August 1998 to March 2000 was analyzed. Twenty nine of these had bronchoalveolar lavage and the respiratory pathogens have been presented. In this study, bacterial and *Pneumocystis carinii* pneumonia are equally important etiologies, but tuberculosis appears to be a more frequent pathogen in our HIV/AIDS population than is reported in the United States. A larger study is needed to confirm our finding and thus to clarify whether an initial presumption of tuberculosis should be assumed when dealing with a Puerto Rican HIV population.

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