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***Pneumocystis* Pneumonia in Hospitalized Patients; A Detailed Examination of Symptoms, Management, and Outcomes in HIV-infected and HIV-uninfected Persons**

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Abstract

Background—*Pneumocystis jiroveci* pneumonia is a life-threatening infection for immunocompromised individuals. There are robust data and clear guidelines for prophylaxis and treatment of HIV-related *Pneumocystis jiroveci* pneumonia (HIV-PCP), yet few data and no guidelines for non-HIV related *Pneumocystis* pneumonia (NH-PCP). We postulated that prevention and inpatient management of HIV-PCP differed from NH-PCP.

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Methods—We performed a retrospective case review of all pathologically confirmed cases of PCP seen at the University of Alabama Medical Center from 1996 to 2008. Data on clinical presentation, hospital course, and outcome were collected using a standardized data collection instrument. Bivariate analysis compared prophylaxis, adjunctive corticosteroids, and clinical outcomes between patients with HIV-PCP and NH-PCP.

Results—Our analysis of the cohort included 97 cases of PCP; 65 HIV and 32 non-HIV cases. Non-HIV cases rarely received primary prophylaxis (4% vs. 38%, $p=0.01$) and received appropriate antibiotics later in the course of hospitalization (5.2 vs 1.1 days, $P<0.005$). Among transplant patients, NH-PCP was diagnosed a mean of 1,066 days after transplantation and most patients were on low-dose corticosteroids (87%) at the time of disease onset. No significant differences in adjunctive corticosteroid use (69% vs. 77%, $p=0.39$) and 90-day mortality (41% vs. 28%, $p=0.20$) were detected.

Conclusions—Patients who have undergone organ or stem cell transplant remain at risk for PCP for many years after transplantation. In our cohort, patients who developed NH-PCP were rarely given prophylaxis and initiation of appropriate antibiotics was significantly delayed compared to cases of HIV-PCP. Medical providers should be aware of the ongoing risk for NH-PCP, even late after transplantation, and consider more aggressive approaches to both prophylaxis and earlier empiric therapy for PCP.

Keywords

Pneumocystis Pneumonia; Transplant; Infectious Complications

Introduction

The early AIDS epidemic fueled major advances in prevention and management of HIV-related *Pneumocystis* pneumonia (HIV-PCP) (1-4). Specifically, antimicrobial prophylaxis and the use of adjunctive corticosteroids for treatment of severe disease have reduced PCP incidence and mortality in HIV-infected persons (5-7).

Although once a rare infection, non-HIV related *Pneumocystis* pneumonia (NH-PCP) is now a growing problem in the United States. Recent data from the Transplant Associated Infection Surveillance Network has indicated that *Pneumocystis* pneumonia complicates 1% of solid organ transplants and has a cumulative incidence of 0.1% per year for stem cell transplant recipients (8, 9).

Prevention and management of *Pneumocystis* pneumonia in HIV-uninfected patients is less clearly defined. Controversy remains regarding the appropriate patient population and duration of prophylaxis against non-HIV related *Pneumocystis* pneumonia (NH-PCP) (5, 6, 10). Similarly, literature on the use of adjunctive corticosteroids in HIV-uninfected patients has shown conflicting results(11-15). While recent reports suggest that adjunctive corticosteroids for NH-PCP has become more common, there are no recommendations or standards of care for adjunctive therapy in these patients(16, 17).

The primary objective of this investigation was to describe the prophylaxis practices, diagnosis, and treatment of NH-PCP as compared to HIV-PCP at a tertiary care hospital over a twelve-year period. We hypothesized that there may be differences in the use of antibiotic prophylaxis and inpatient management between patients who develop NH-PCP and HIV-PCP.

Methods

The University of Alabama at Birmingham (UAB) Hospital is a 900-bed, tertiary care, urban, teaching hospital with diverse medical and surgical patient populations. The hospital routinely provides Hematology and Oncology services, Trauma and Burn Surgical services, General Medical services, General Surgical services, and has large, active Bone Marrow and Solid Organ Transplantation programs. UAB Hospital is also affiliated with an outpatient HIV-clinic that serves over 1,800 HIV-infected persons (18). Duration and antibiotic selection for PCP prophylaxis is left to the discretion of the treating clinician.

The Department of Pathology at UAB maintains an electronic database for all pathology reports since January 1996. We queried this database for pathology reports for all pulmonary specimens (sputum, bronchoalveolar lavage, transbronchial biopsy, or surgical lung biopsy specimens) submitted to the Department of Pathology from January 1, 1996 through November 30, 2008. Reports for all pulmonary specimens were independently reviewed (J.M., A.C.) for cytologic identification of *Pneumocystis* organisms with methenamine silver staining or immunofluorescence. Discrepancies were resolved by consensus. Patients with a presumed diagnosis of PCP, yet lacked pathologic confirmation of the diagnosis were not included. Diagnostic procedure used to obtain pulmonary specimens (i.e. induced sputum, bronchoalveolar lavage, transbronchial biopsy, or surgical procedure) was determined at the discretion of the treating physician.

Medical records for all patients with pathologically confirmed PCP were reviewed (J.M., A.C.). A standardized chart abstraction instrument was used to collect data on demographic information, presence of co-morbidities, clinical presentation, selection and time to initiation of effective antimicrobial treatment, utilization of adjunctive corticosteroids, and outcomes. The following definitions were used: cancer – any active malignancy; hypoxia- oxygen saturation <85% or partial pressure of oxygen <70 mm Hg, or treatment with >30% oxygen supplementation; abnormal white blood cell count – >12,000 cells/mm³ or <4,000 cells/mm³; concurrent infection - positive blood culture for bacteria or fungi, positive serum assay for pp65 (Cytomegalovirus), or evidence of additional pneumonic process based on pathologic exam or culture from deep pulmonary isolate during the hospitalization.

Effective antimicrobial therapy for PCP was defined as use of trimethoprim/sulfamethoxazole (TMP/SMX), primaquine/clindamycin, pentamidine, or atovaquone. Corticosteroids were classified as low-dose therapy (<1mg/kg) or high-dose therapy (1mg/kg), as previously defined (11). The primary outcome of interest was all-cause mortality at 90 days from hospital admission. Mortality was determined from hospital records and social security databases. Secondary outcomes were time to resolution of hypoxia (defined previously) and in-hospital mortality.

Statistical analyses

Frequencies of categorical variables and means, medians and standard deviations of continuous variables were calculated for the overall population, and for patients with HIV infection and for patients without HIV. For the comparison of variable frequencies in patients with and without HIV, bivariate analyses were performed using chi-square or Fisher's exact methods as appropriate for categorical variables and student's t-test or the Wilcoxon rank sum test as appropriate for continuous variables. Statistical tests were two-tailed and were performed using a 0.05 significance level. Statistical analyses were conducted using SAS (version 9.1; SAS Institute, Inc., Cary, NC). The University of Alabama at Birmingham Institutional Review Board approved this study.

Results

Over the study period, 101 patients had a definitive diagnosis of *Pneumocystis jirovecii* pneumonia. There were 69 HIV related cases and 32 non-HIV related cases. Four cases of HIV-PCP were excluded from the analysis due to incomplete medical records (n=2) or receipt of unknown therapy at an outside hospital (n=2). The mean CD4 count in the HIV-infected cohort was 12 cells/mm³ (range 1-84 cells/mm³).

Underlying conditions in the NH-PCP cohort included solid organ transplant (n=19; Heart 8, Heart/Lung 2, Lung 6, Heart/Kidney 1, Kidney 2), stem cell transplant (n=4; Multiple Myeloma 1, Hodgkins Lymphoma 2, Non-Hodgkins Lymphoma 1), neoplasm (n=4, Breast 2, Leukemia 2), and other conditions (n=5; Common Variable Immunodeficiency 1, COPD/Diabetes 1, Stills Disease 1, No Underlying Conditions 2). All patients with NH-PCP were HIV-seronegative. Day of transplantation was available for most patients (83%, 19/23). Time between transplantation and hospital admission for PCP was a mean of 1,066 days with a median of 638 days (range: 247-4,077). Most transplant patients (87%, 20/23) were receiving low-dose corticosteroids during the 30 days preceding admission. Compared to HIV-infected persons, patients with NH-PCP infrequently received prophylaxis prior to admission (38% vs. 4%, p=0.01) (Table 1).

Clinical Presentation and Diagnosis

The clinical presentation of NH-PCP and HIV-PCP was relatively similar. Both populations had documented reports of cough (68% vs. 87%, p=0.03), dyspnea (75% vs. 83%, p=0.36), and fever (66% vs. 75%, p=0.33). HIV-uninfected patients had fewer reported complaints of chest pain/pleuritic pain (6% vs. 28%, p=0.01) and weight loss (9% vs. 28%, p=0.03). Patients with NH-PCP reported shorter duration of illness, fewer days of dyspnea (10±2 vs. 17±2 days; p=0.02) and fever (8±2 vs. 15±4 days; p=0.02) (Table 2).

There were few objective differences in the severity of illness on presentation (Table 2). Patients in both cohorts were found to have tachypnea (22±1 bpm for NH-PCP vs. 22±1 bpm for HIV-PCP, p=0.62), tachycardia (107±3 bpm vs. 111±3 bpm, p=0.62), hypoxia (53% vs. 51%, p=0.83), and low-grade temperature elevations (99°±0.3°F vs. 100°±0.3°F, p=0.03). Chest roentography typically demonstrated bilateral evidence of disease (67% vs. 66%, p=0.86). Sensitivity analysis of oxygen saturation, partial pressure of oxygen, and use of supplemental oxygen considered independently showed no differences between the two groups. Statistically, there were no differences with regards to peripheral leukocyte count or lactate dehydrogenase (Table 2).

Method of diagnosis and diagnostic yield of invasive testing was similar between the two groups. Time from admission to diagnosis was similar between NH-PCP and HIV-PCP (4.3±0.9 days vs. 3.7±0.4 days, p=0.9). Bronchoscopy with transbronchial biopsy was the most common test performed, and was usually diagnostic in both cohorts. Bronchoalveolar lavage without biopsy was diagnostic in 1 of 3 patients (33%) with NH-PCP and 4 of 9 patients (44%) with HIV-PCP. (Figure 1)

Treatment and Outcomes

The most common treatment for PCP was TMP/SMX in both cohorts (72% vs. 71%, p=0.91). Providers used adjunctive corticosteroids in the management of NH-PCP and HIV-PCP individuals (69% vs. 77%, p=0.39). All patients classified as “hypoxic” were given adjunctive corticosteroids. HIV-uninfected patients had antimicrobials initiated significantly later (5±1 vs. 1±0.3 days, p=0.005) (Table 3).

With regards to therapy response, time from starting anti-PCP therapy to resolution of hypoxia was similar between the two groups (10 ± 1.0 days for NH-PCP vs. 9 ± 0.8 days for HIV-PCP, $p=0.65$). Both patient groups had similar rates of in-hospital (27% vs. 19%, $p=0.43$) and 90-day all cause mortality (41% vs. 28%, $p=0.20$) (Table 3).

Discussion

This investigation is a 12-year, retrospective study of all pathologically confirmed cases of *Pneumocystis* pneumonia admitted to a tertiary medical center. Our data highlight important gaps in our understanding of non-HIV related PCP, particularly pertaining to appropriate antibiotic prophylaxis and inpatient management. Findings from this investigation indicate important areas for future investigation and provide clinically relevant patient information to help guide clinician decisions, particularly in the transplant population.

The current approach to patient selection for PCP prophylaxis and duration of prophylaxis for non-HIV infected persons is highly variable and there is no consensus approach to this issue (5, 6, 10). For example, primary prophylaxis against PCP is routine for many medical centers following renal, cardiac, lung and liver transplants (10). However, some centers recommend as little as 6 months of prophylaxis, while others recommend 12 months or even lifelong prophylaxis (19).

The majority of NH-PCP patients in our cohort were not receiving PCP primary prophylaxis prior to admission. The median time between transplantation and PCP diagnosis was two years with a range of 8 months to 11 years. Most patients were on stable and low-dose corticosteroids for the 30 days prior to admission. Until results of more definitive, controlled studies and risk-benefit analyses become available, our data suggest prolonged prophylaxis for transplant recipients as a means to prevent this life-threatening infection (19).

Our data also suggest that there may be additional risk factors and potentially specific immune defects associated with NH-PCP infection other than the traditional risk factors of corticosteroid dose and time from transplantation. A laboratory-based assay to evaluate immune function would represent an important adjunct in determining need for prophylaxis against NH-PCP. The peripheral blood CD4 count has proven to be an important indicator of PCP risk in the HIV-infected patient (5). There are preliminary data to suggest that low peripheral blood CD4 count may also help identify immunocompromised patients (without HIV infection) at risk for PCP(20). The role of the peripheral CD4 count in predicting NH-PCP remains to be defined but additional investigation appears warranted. Further research is also needed to understand the role of colonization with *Pneumocystis jirovecii* among immunosuppressed patients as a possible predictor of subsequent PCP(21).

There were a number of differences in clinical presentation and inpatient management of NH-PCP and H-PCP. Delayed initiation of antibiotics was an important observation of our investigation. Time from admission to diagnosis was approximately four days for HIV-infected and HIV-uninfected patients. However, antibiotic therapy for PCP was typically initiated on hospital day 1 for H-PCP, but hospital day 5 for NH-PCP. We were unable to find an association between time to antibiotics and clinical outcome (data not shown), but we suspect that earlier, empiric therapy would improve clinical outcomes in the NH-PCP group.

Similar to previous investigations, we observed that the duration of symptoms was typically shorter for patients with NH-PCP (22, 23). However, unlike previous reports, we found relatively few differences in objective measures of disease severity on hospital admission including respiratory rate, need for mechanical ventilation, LDH, or our composite endpoint

of hypoxia (11, 16, 22-24). Our observed data suggest that the epidemiology of PCP may be changing, but should be confirmed with investigations from different institutions and a broader patient distribution.

No prospective investigations on the role of adjunctive corticosteroids in NH-PCP have been conducted. Given the rarity of PCP in HIV-uninfected individuals, it is unlikely that a prospective randomized trial will ever be conducted. Most retrospective studies have shown either a benefit (11-13) or no impact (14) with increasing corticosteroids in NH-PCP. However, some clinicians remain hesitant to increase corticosteroid dosage in persons with hypoxia due to NH-PCP (16, 17). In our cohort, we found frequent use of adjunctive corticosteroids in patients with H-PCP (77%) and NH-PCP (69%). All patients with hypoxia at the time of diagnosis were given adjunctive corticosteroids.

Failure to increase corticosteroid dosage in NH-PCP may have implications for patient mortality. Previous investigations comparing *Pneumocystis* pneumonia in HIV-infected and HIV-uninfected patients found higher mortality in patients with NH-PCP (11, 16, 22, 25). However, these investigations were conducted in an era when utilization of adjunctive corticosteroids was primarily limited to patients with HIV-PCP. More recent investigations have observed increased use of adjunctive corticosteroids in NH-PCP and similar mortality between HIV-PCP and NH-PCP (16, 17). Authors of these studies hypothesized that increased use of adjunctive corticosteroids in NH-PCP may have closed this survival gap.

There are limitations to our investigation. Although our investigation represents a large cohort of patients with PCP, data were collected retrospectively from a single center (UAB Medical Center) and we were unable to abstract, describe, and analyze all datapoints for all patients. As a result, some of our analyses were limited by small variable frequencies. Furthermore, our observations may not be a true representation cases presenting at other centers. Our study also did not evaluate treatment of concurrent infections or management of other medical complications in both groups. Finally, excluding suspected cases may have led to selection bias of the population.

In summary, our 12-year retrospective review of *Pneumocystis* pneumonia at a large tertiary medical center, provides important insights by highlighting the clinical impact of gaps in our understanding of NH-PCP. Our finding that PCP may occur late after transplantation supports the need for further research into risk-stratification and cost-benefit analysis to determine the appropriate duration of prophylaxis against NH-PCP (19). Consistent with previous reports, adjunctive corticosteroids were used frequently for both NH-PCP and HIV-PCP (16, 17). However, our observation that appropriate antibiotic therapy was delayed in the NH-PCP cohort is novel and warrants further investigation as it may have an impact on patient outcomes. Given the growing use of immunosuppressant medications such as tumor necrosis factor-alpha inhibitors and the burgeoning population of transplant patients, NH-PCP will remain a challenging problem for clinicians. Further study on this important topic is needed to increase provider awareness and to define optimal prevention and treatment.

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Abbreviations

HIV-PCP	<i>Pneumocystis</i> pneumonia that develops in a patient with underlying HIV disease
NH-PCP	<i>Pneumocystis</i> pneumonia that develops in a patient without underlying HIV disease
UAB	The University of Alabama at Birmingham
PCP	<i>Pneumocystis jirovecii</i> pneumonia
TMP/SMX	Trimethoprim-Sulfamethoxazole

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Figure 1.

Diagnostic approach and yield of invasive testing for NH-PCP and for HIVPCP. HIV, Human immunodeficiency virus; NH-PCP non-HIV-related *Pneumocystis pneumonia*; HIV-PCP, HIV-related *Pneumocystis pneumonia*; BX, transbronchial biopsy; VATS, video-assisted thoracic surgery.

Table 1

Patient Characteristics of HIV and Non-HIV Related *Pneumocystis* Pneumonia at the University of Alabama at Birmingham.

	NH-PCP (N=32)	HIV-PCP (N=65) ¹	P-Value
Patient Characteristics			
Age	51.0 ± 16.1 Years	38.5 ± 8.5 Years	P=<0.001
Sex (Male)	18/30 (60%)	42/65 (65%)	P=0.82
Race (Non-white)	6/32 (19%)	38/65 (58%)	P=0.002
PCP Prophylaxis	2/25 (4%)	19/50 (38%)	P=0.01
Underlying Diseases ²			
-Solid Transplant	19/32 (59%)	0/65	
-Stem Cell Transplant	4/32 (13%)	0/65	
-Neoplasm	4/32 (13%)	0/65	
-Other	5/32 (15%)	0/65	

-NH-PCP: Non-HIV Related *Pneumocystis* Pneumonia; HIV-PCP: HIV Related *Pneumocystis* Pneumonia

¹ Mean CD4 Count= 11.6 cells/mm³ (Range=1-84 cells/mm³)

² Underlying conditions Included-Solid Organ Transplants (n=19): Heart (8), Heart/Lung (2), Lung (6), Heart/Kidney (1), Kidney (2)

Stem Cell Transplant (n=4): Multiple Myeloma (1), Hodgkins Lymphoma (2), Non-Hodgkins Lymphoma (1)

Neoplasm (n=4): Breast (2), Leukemia (2)

Other Causes (n=5): Common Variable Immunodeficiency (1), COPD/Diabetes (1), Stills Disease (1), No Underlying Conditions (2)

Table 2

Clinical Presentation of HIV and Non-HIV Related *Pneumocystis* Pneumonia at the University of Alabama at Birmingham.

	NH-PCP (N=32)	HIV-PCP (N=65)	P-Value
Symptomatology and Clinical Presentation			
-Cough	22/32 (68%)	57/65 (87%)	P=0.03
-Dyspnea	24/32 (75%)	54/65 (83%)	P=0.36
-Fever	21/32 (66%)	49/65 (75%)	P=0.33
-Chest Pain	2/32 (6%)	18/65 (28%)	P=0.01
-Wt Loss	3/32 (9%)	18/65 (28%)	P=0.03
Symptom Duration			
-Cough	9.86 ± 1.70 days	15.2 ± 1.72 days	P=0.08
-Dyspnea	9.88 ± 1.54 days	17.3 ± 1.91 days	P=0.02
-Fever	8.05 ± 1.57 days	15.4 ± 3.67 days	P=0.02
-Chest Pain	1.00 ± 1.00 days	9.55 ± 1.53 days	P=0.02
-Wt Loss	10.3 ± 6.06 days	110 ± 28.0 days	P=0.04
Vitals			
-Temperature (°F)	99.0° ± 0.30	100.0° ± 0.25	P=0.03
-Pulse (BPM)	107 ± 3.13	111 ± 2.84	P=0.39
-Respiration (BPM)	21.7 ± 1.17	22.1 ± 0.70	P=0.62
AMS	0/30 (0%)	7/65 (11%)	P=0.09
LDH (U/L)	354.9 ± 29.2	496 ± 50.5	P=0.10
WBC, abnormal ¹	8/30 (27%)	14/65 (22%)	P=0.65
CXR, bilateral	21/32 (67%)	43/65 (66%)	P=0.86
Hypoxic ²	17/32 (53%)	33/65 (51%)	P=0.83
-Mechanical Ventilation	4/32 (13%)	7/65 (11%)	P=0.80
-100% Non-Rebreather Facemask	5/32 (16%)	6/65 (9%)	P=0.35

-NH-PCP: Non-HIV Related *Pneumocystis Pneumonia*; HIV-PCP: HIV Related *Pneumocystis Pneumonia*

¹ WBC abnormal when >12,000 cells/mm³ or <4,000 cells/mm³

² Hypoxic when oxygen saturation <85%, partial pressure of oxygen <70 mm Hg, or treatment with >30% oxygen supplementation

Table 3

Diagnosis, Treatment, and Clinical Outcomes of HIV and Non-HIV related *Pneumocystis* Pneumonia at the University of Alabama at Birmingham.

	NH-PCP (N=32)	HIV-PCP (N=65) ^I	P-Value
Diagnosis and Treatment			
Time from Admission to Diagnosis	4.28 ± 0.94 days	3.69 ± 0.38 days	P=0.9
Time From Admission to Therapy	5.19 ± 0.95 days	1.10 ± 0.27 days	P<0.005
TMP/SMX Rx	23/32 (71.9%)	46/65 (70.8%)	P=0.91
Other	9/32 (28.1%)	19/65 (29.0%)	P=0.95
-Pentamidine	1	6	
-Dapsone	1	1	
-Primaquine/Clinda	5	9	
-Atovaquone	2	3	
Adjunctive Corticosteroids	22/32 (68.8%)	50/65 (76.9%)	P=0.39
Clinical Outcomes			
Duration of Hypoxia^I	10.1 ± 1.04 days	9.3 ± 0.78 days	P=0.65
Coinfection	14/32 (44%)	31/65 (48%)	P=0.88
-CMV	6	14	
-Pneumonia	7	11	
-BSI	6	14	
In Hospital Mortality	8/30 (26.7%)	12/63 (19.0%)	P=0.43
-Respiratory	7/8	11/12	
-Unknown	0/8	1/12	
-Sepsis	1/8	0/12	
90-Day Mortality	13/32 (40.6%)	18/65 (27.7%)	P=0.20

-NH-PCP: Non-HIV Related *Pneumocystis Pneumonia*; HIV-PCP: HIV Related *Pneumocystis Pneumonia*

^IDuration of hypoxia was measured from the initiation of PCP therapy. Abbreviations-TMP/SMX: Trimethoprim Sulfamethoxazole, BSI: Bloodstream Infection