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THE SPECTRUM OF RADIOLOGICAL APPEARANCES IN BRONCHOSCOPICALLY PROVEN PNEUMOCYSTIS PNEUMONIA IN HIV POSITIVE ADULTS:
A retrospective analysis from Helen Joseph Hospital

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Diagnostic Radiology.

Johannesburg, 2011

Declaration

I, Grace Rubin, declare that this research report is my own work. It is being submitted for the degree of MMed (RadD) in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

DR G RUBIN

On this..... day of..... 2011.

Dedication

To my mother and father, Dr Joseph and Janet Rubin,

for inspiring a love of learning.

To Professor Elaine Joseph for inspiring this study.

Publications and Presentations

This work has never been published or presented previously.

Abstract

Pneumocystis jirovecci pneumonia (PJP) in HIV/AIDS is a significant opportunistic infection. As CD4 counts decrease, so does specificity of chest X-ray (CXR).

AIM: To determine the proportion of bronchoscopically proven PJP in HIV infected adults, CD4 counts, CXR signs and compare PJP to TB.

METHODS: The proportion of bronchoscopically proven PJP and co-infection was determined. Sensitivity and specificity of CXR for the diagnosis of PJP and TB, and frequency of CXR signs were determined.

RESULTS: PJP was present in 26.6% and co-infection 19%. Median CD4 (13 cell/mm^3) was significantly lower for PJP patients ($p = 0.0089$). CXR sensitivity for PJP was 33% and specificity was 100%. Bilateral, multilobar and diffuse disease, bronchopneumonia, nodules and cavitation overlapped for PJP and TB. Unilateral and unilobar disease indicated TB over PJP. Effusions and lymphadenpopathy were not seen with PJP.

CONCLUSION**:** PJP makes up a quarter of indeterminate diagnoses in HIV infected adults. Sensitivity of diagnosis on CXR is low. The CXR diagnosis of TB is made more confidently, but is overcalled. In patients with low CD4 levels, a diagnosis of PJP should be considered as important as TB.

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CHAPTER ONE

INTRODUCTION

1 INTRODUCTION

1.1 Overview

Pneumocystis pneumonia or *Pneumocystis jirovecii* pneumonia (PJP) in the setting of Human immunodeficiency virus (HIV) and Acquired immunodeficiency syndrome (AIDS) is still a significant opportunistic infection worldwide, despite the advent of antiretroviral therapy (1,2). It typically presents in patients with low CD4 counts below 200cells/mm^3 (2,3, 4). Pneumocystis Pneumonia carries a high morbidity and mortality rate and its diagnosis is imperative for timeous and effective antimicrobial therapy (1,2, 5). PJP still remains a common initial presenting illness in HIV infected individuals in the developed world in a background where a significant percentage of patients are unaware that they have HIV infection (from 2001 – 2006 rates of HIV testing in the USA show only 40% of the population ever tested) (6) . Though having decreased dramatically, opportunistic infections (OIs) remain one of the main causes of hospitalization and death in HIV infected people (6).

In the developing world Pneumocystis pneumonia has been thought to be an uncommon pulmonary opportunistic infection especially in the light of the widespread rates of tuberculosis (TB) and bacterial pneumonias due to HIV/AIDS (2). More recent reports are emerging, however, revealing PJP's more commonplace prevalence (1). As CD4 count deteriorates so does the specificity of chest X-ray (CXR) findings making the diagnosis of specific pulmonary infection all the more difficult (7). There is also overlap of radiographic signs within the spectrum of HIV pulmonary disease as well as coexistence of more than one pathogen in a single patient presenting with disease (4,7). The lack of availability and

access to laboratory and bronchoscopic resources to confirm PJP infection is thought to have in part contributed to the under-reporting of Pneumocystis pneumonia in HIV/AIDS in Africa (2).

In reports emerging from African medical literature, CXR's read blind by radiologists were over reported as TB and not as PJP, where bronchoscopy results of these patients showed PJP infection rather than TB (8). In HIV/AIDS patients with low CD4 counts , non-specific CXR patterns have been seen which have been misinterpreted as TB or a non specific CXR diagnosis was made (9).

1.2 Global HIV and HIV in South Africa

At the end of 2008, 33.4 million people worldwide were estimated to be living with HIV/AIDS according to UNAIDS2009 (10). Although the prevalence rate has levelled off, numbers of people living with the disease have continued to increase, as estimated AIDS-related deaths decrease (approximately 10% lower in 2008 than in 2004)(11). In 2008, 2.7 million new infections occurred worldwide (30% lower than during the epidemic's peak in 1996) (10). Women comprise half of adults living with HIV/AIDS worldwide and young people under 25 yrs of age account for more than half of all new HIV infections (11). In contrast to 2.3 million people living with HIV/AIDS in North America and Europe documented for 2008, there were 4.2 million in South/South-East Asia living with HIV/AIDS (10).

There is not a homogenous AIDS epidemic but a worldwide diversity of AIDS by region or country. Sub-Saharan Africa accounts for only 12% of the world's population, yet has the majority of people living with HIV/AIDS (22.4 million- and a 5.2% prevalence) (10). HIV is the leading cause of death in the region, with Southern Africa the worst affected.

With more than 5.7 million people living with HIV/AIDS, South Africa has a prevelance rate of 16.9% and the world's largest population of people with HIV infection (10). The first case of HIV/AIDS in South Africa was reported in 1982 (12). The prevalence rate in SA is significantly higher than the overall rate in Sub-Saharan Africa and globally. Overall death rates in South Africa have increased by 80% - largely due to HIV/AIDS (12). In 2007 there were 350 000 AIDS deaths in South Africa and AIDS was estimated to have accounted for nearly half of all deaths in 2006 (12).

The overall picture shows a change. The 1.4 million AIDS – related deaths in 2008 in Sub-Saharan Africa, represents an 18% decline in annual HIV– related mortality since 2004 (10). Between 2003 and 2008 access to antiretroviral drugs increased 10-fold in middle and low income countries. This has reduced mortality related to HIV by half in a treatment centre in the Western Cape between 2001 – 2005, as patients with less immunosuppression joined the program (11).

However, the South African Department of Health states that 'there is no evidence of a decline in new HIV infections, 29% of pregnant women accessing public health services tested HIV positive in 2008' (10). Notably, there were also over 1 million AIDS orphans in South Africa by the end of 2007 (12).

Reflected in the epidemiology since a quarter century ago, when Pneumocystis pneumonia heralded the onset of the AIDS epidemic, there has been a shift in the presentation of HIV/AIDS with the majority of new cases occurring in the developing world (1,11,12,13). In the developed world, opportunistic infections are diminishing in frequency, whereas in other settings, where there is reduced access to antiretroviral therapy, opportunistic infections remain frequent (11). This has led to differences in presentation of HIV-related pulmonary disease across the globe, notably the difference in the developed versus the developing world, and this will be explored in the South African context.

1.3 Antiretroviral Therapy

The advent of highly active anti retroviral therapy (HAART) has allowed for immune reconstitution with prolonged viral suppression and reductions in rates of opportunistic infections and AIDS as well as related reduction of mortality in Europe and North America(1). From 1996-2004, in10 USA cities, caring for 3000 infected HIV patients per year, AIDS-related deaths were shown to have dropped from 7 deaths/100 person years to 1.3 deaths/100 person years (14). This correlated directly with an increased HAART utility from 43% of patients in 1996 to 82% in 2004 in the same study. Immune reconstitution due to HAART has given rise to the improved mortality and morbidity from conditions such as cytomegalovirus and Kaposi's sarcoma, where specific OI preventive measures have not been available (15). Long term use of HAART and higher CD4 cell counts are now associated with death from 'non-AIDS' illnesses such as chronic viral hepatitis, hypertension, cardiovascular disease, diabetes and pulmonary diseases as well as non-AIDS malignancies similar to the general community (14).

Similar benefits have been seen in South Africa, Zambia, Uganda, South East Asia and Latin America where such programs are delivering antiretroviral therapy (10). Overall 2, 120 000 people received HAART in Sub-Saharan Africa as of December 2007. This means that 70% of those in need of HAART in Sub-Saharan Africa have not yet accessed therapy. In South Africa itself 460 000 people living with HIV/AIDS (approximately 10% of the HIV population) were receiving HAART by end of 2007 (1,11,12). According to UNAIDS 2009, South Africa now has implemented the largest antiretroviral therapy program in the world to reduce mortality from HIV disease and related infections (11). There are suspected high numbers of people living with HIV and not taking ARV's. This is most likely due to a combination of factors, including lack of information about ARV's, lack of knowledge of personal HIV status, diminished societal awareness of HIV and its processes of transmission (although recent improvements to this have been made), and/ or non-compliance with ARV medication. This correlates with data reported in 2008 from ante-natal clinics in Johannesburg where the mean baseline CD4 count was 154 cells/mm^3 which indicates advanced disease (12, 16). Similar findings were reported in 2009, with a mean CD4 count at first time presentation at an urban HIV clinic in Soweto of 109cells/mm^3 in the female population (17). Undetected and later presentation of HIV/AIDS, as well as non- accessed HAART, contribute to the particular disease pattern and frequency of opportunistic infections seen in South Africa and sub-Saharan Africa.

1.4 Opportunistic infections in HIV/AIDS

1.4.1 Epidemiology of Opportunistic infections

In the USA and developed world, the incidence of opportunistic infections (OI) has decreased definitively from 1992. This is probably due to the introduction of combination antiretroviral therapy as it has become simpler, more effective and less toxic (1,6,15).

The high mortality in HIV infected patients in Sub Saharan Africa relates to the low CD4 counts at presentation (13). A high early mortality of between 8-26% of patients within the first year of starting antiretrovirals is found in patients with baseline CD4 counts of 50cells/mm^3 and less (2). OI's are the major cause of mortality in these patients (1). HIV has fuelled the TB epidemic that has expanded globally, and its incidence is several hundred times greater in the AIDS population than the general population (3). In 2006, 9.2 million new cases of TB occurred worldwide. Over a third of these cases were in Africa and 38% of the 1.7 million worldwide deaths occurring from TB in this period were accounted for by the World Health Organzation (WHO) for the Africa Region. Thirteen out of 15 countries with the highest incidence of TB were from Africa (1). Despite the availability of HAART 'Pneumocystis pneumonia remains a leading cause of morbidity and mortality' (18) and bacterial and other fungal opportunistic infections continue to remain commonplace (7).

1.4.2 Pulmonary manifestations of HIV/AIDS

In a review of thoracic AIDS in 2002, pulmonary manifestations of HIV disease were common and accounted for 30-40% of acute admissions to a London hospital (3). In the developed world the commoner OI's cited for discussion in patients with AIDS in the era

of HAART included bacterial pneumonias, Pneumocystis pneumonia, *Mycobacterium tuberculosis*, *Cryptoccoal neoformans* infection, *Mycobacterium avium complex* (MAC*)* and cytomegalovirus (CMV). All are seen with higher frequency in HIV positive patients and are seen with increased frequency as CD4 counts drop below 200cells/mm.[3]The increasing risk for all pneumonias is associated with decreasing CD4 counts, and clinically apparent recurrent bacterial pneumonias continue to be the commonest, occurring before and after the onset of AIDS (3). TB remains the commonest opportunistic pneumonia in sub- Saharan Africa while bacterial pneumonia is the most frequent opportunistic pneumonia in the United States and Western Europe (19). Pneumocystis pneumonia is the commonest AIDS-related OI in the United States, and together with TB, is the commonest OI in Western Europe, now in the HAART era (19). The overall incidence of PJP due to ART and PJP prophylaxis is on the decline in the United States.

PJP has been increasingly reported in sub-Saharan Africa where it had been previously thought to be a rare pathogen. TB remains the dominant OI in Africa and in low and middle income countries (19). In both settings, PJP remains a 'persistent and deadly opportunistic infection' (20).

1.4.3 PJP as a Pulmonary Opportunistic Infection in HIV/AIDS

Despite availability of HAART, Pneumocystis pneumonia continues to cause significant morbidity and mortality in HIV- infected populations. It occurs in patients unaware that they have HIV, who are not on ARV's and present with OI as the initial presentation of late HIV disease (18). Poor adherence to HAART, economic, psychosocial, biological factors and unexplained resistance, all prevent efficacy of ARV's (6). Rates of HIV testing in the USA in a 2001-2006 survey indicate that only 40% of surveyed adults aged 18-64 had ever been tested (6). This could explain, in part, the presentation of as many as 25-50%

of HIV patients with CD4<200cells/mm^3 at first diagnosis, at both rural and inner urban HIV clinics within the USA (6). In the Developed world, PJP is still the initial presentation of HIV in the HAART era, in 37% of patient compared to 39.3% in the pre HAART period 1990-1995. This was shown in a multicentre study done in the USA, and PJP was associated with a high mortality rate (37% in the HAART period and 45% in the pre-HAART era). In the same review, only a third of patients received PJP prophylaxis at any one time, and mortality was found to be higher in patients not taking prophylaxis (20).

1.5 The CXR in pulmonary infections in HIV/AIDS

1.5.1 Relevance of the CXR

A plain CXR together with a clinical assessment remains the starting point and mainstay investigation of opportunistic chest infections, in conjunction with the patient's CD4 count. These, together, act as diagnostic guidelines. Computed Tomography (CT) is usually not required except as a problem solving tool (3). Despite the diagnostic indicators of radiographic patterns, CD4 counts, and clinical symptomatology, considerable overlap and atypical radiological presentation is encountered (3, 7). This is confounded by a differential diagnosis which also includes non infectious HIV/AIDS pathology (3). Imaging on CXR is usually sought, but radiographic patterns on CXR in immunocompromised patients are often nonspecific (4). Indeed, as CD4 levels drop below 200 cells/mm^3 , non specificity of CXR patterns increases (3,4,7). Added to this, it is well documented that a normal CXR does not imply absence of disease in significantly immunocompromised patients, belying the presence of PJP and active TB in 10% and up to 20% of patients respectively (7 ,21). Greenberg et al have shown that clinical evaluation was also not a reliable indicator of disease. In patients who were both HIV infected and TB culture positive, there were between 50-70% false negative tuberculin skin tests and up to

50% negative acid fast bacilli in sputum or bronchoalveolar lavage (BAL). In these patients, the findings of cough, abnormal CXR, haemoptysis and elevated white cell counts prompted investigation (21).

1.5.2 Diagnostic Patterns on CXR

Interpretation of radiographic patterns on CXR narrows the possibilities of potential pathogens. CXR can, however, be non-specific and variable, so the importance of a CD4 count together with symptoms of hypoxia, environmental exposure, HAART / OI prophylaxis and the demographics of the disease are well recognized contributors to diagnosis (1,4,7).

In patients with CD4 > 200cells/mm^3**,** bacterial pneumonias caused by *S pneumoniae, H influenza, S. aureus* and *Pseudomonas aeruginosa* occur, and patients are more likely to acquire invasive pneumoccocal disease (1,3,4) . Studies originating in South Africa (miners) and from Kenya showed that the risk of acquiring pneumonia is clearly associated with decreasing CD4 counts (1). The USA and Europe have experienced a reduction in rates of bacterial pneumonia after the introduction of HAART (1,3, 15). Lobar and segmental consolidation, effusions and the rapid progression of bacterial pneumonias in HIV positive patients give rise to cavitation and atypical infiltrates. This makes differentiation of bacterial pneumonia from TB and PJP difficult (3).TB presents with more typical radiographic patterns of reactivation cavitation, bronchiectasis and bronchovascular distortion in patients with CD4>200/mm^3 (3,4,7,21).

With CD4 100 – 200 cells/mm^3 bacterial pneumonia, primary TB, PJP and fungal infections are encountered, radiological indicators of disease pathogens become less distinct as lobar consolidation and effusion may be manifestations of both primary TB and

bacterial pneumonia (1,3,7). Visible lymphadenopathy on CXR is more suggestive of TB (Figure 1.1) (4)

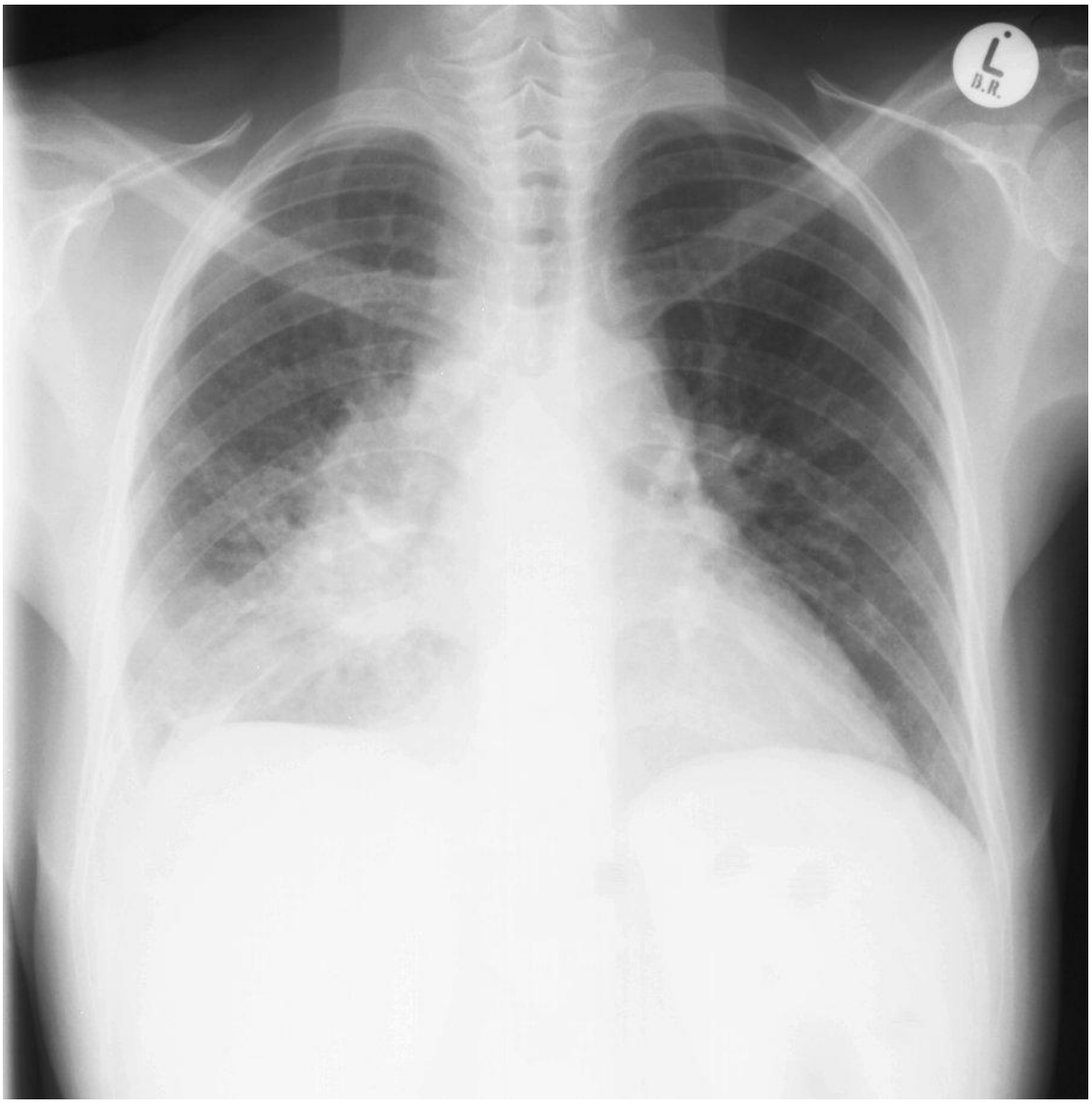


Figure 1.1 Primary TB

Frontal CXR in a 31 yr old female demonstrating right hilar and paratracheal nodes , right middle lobe consolidation and veiling of the right base due to a pleural effusion in a patient with primary TB.

PJP presents typically with diffuse bilateral and perihilar groundglass opacities and thin walled cysts (figure 1.2).The complications of peumothorax/pneumomediastinum may be seen without adenopathy or effusions (1,4). However, multifocal airspace shadowing, thickened reticular and linear infiltrates, mass lesions, nodules, cavitations and even adenopathy are atypical manifestations of PJP (Figures 1.3, 1.4 and 1.5). The possibility of a normal CXR and non-specific CXR patterns in PJP disease makes clinical features such as hypoxia and laboratory features such as CD4<200cells/mm^3 important diagnostically. Acute rate of onset of disease might help point to bacterial pneumonia, oedema or pulmonary haemorrhage, whereas a subacute process over days or weeks are usually viruses , PJP, TB or fungi (7).



Figure 1.2 Typical PJP

Frontal CXR of a 34yr old male with typical features of PJP demonstrating hazy groundglass opacification and fine reticulation bilaterally.



Figure 1.3 Atypical PJP, coarse reticular pattern

Frontal CXR in a 34 yr old female demonstrating atypical PJP with a bilateral diffuse coarse reticular pattern with left upper lobe and lower lobe segmental consolidation.

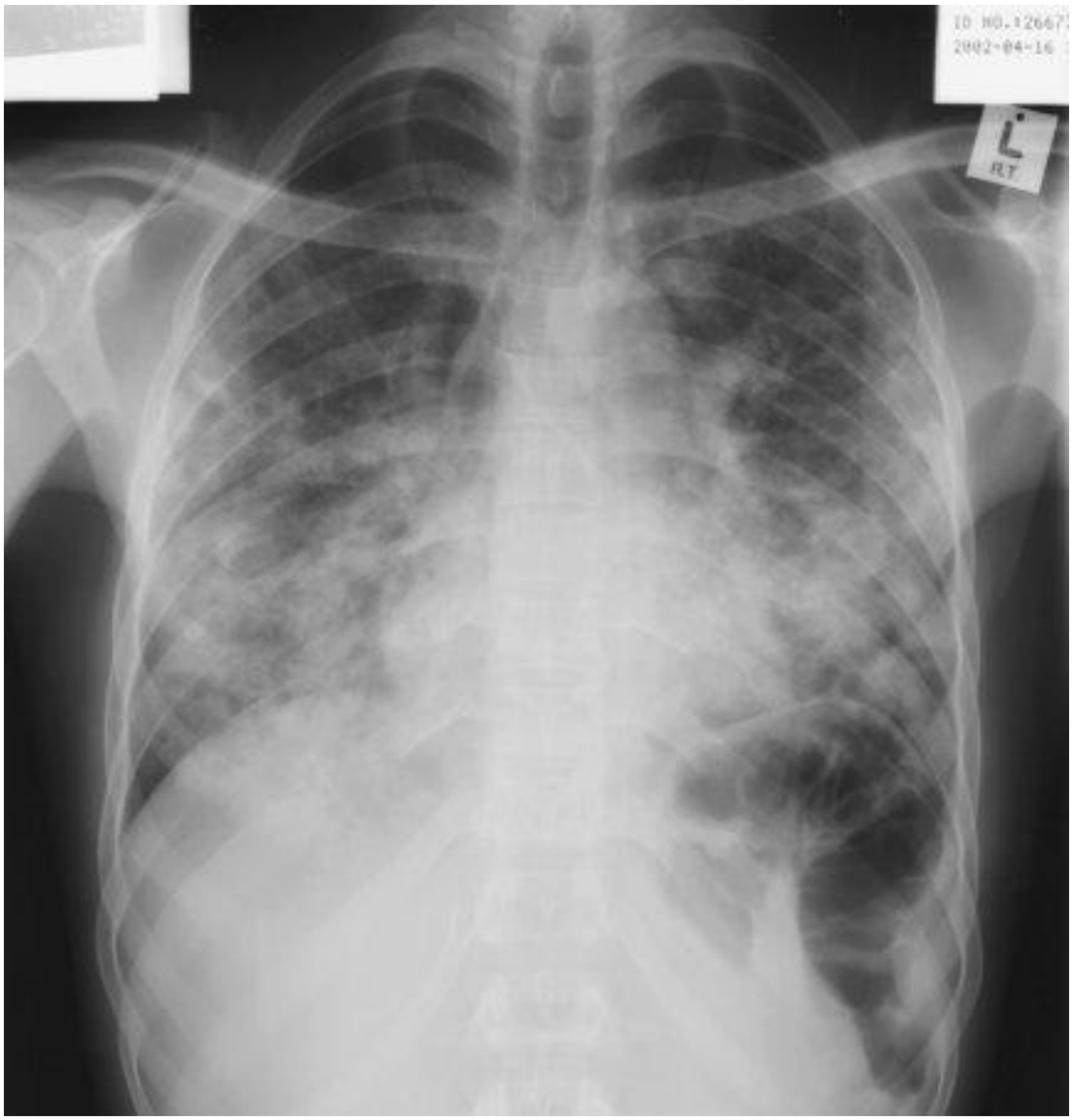


Figure 1.4 Atypical PJP, nodules and consolidation

Frontal CXR in a 32 yr old male demonstrating atypical PJP with bilateral patchy consolidation, coarse reticulation and ill defined large nodules bilaterally.



Figure 1.5 Atypical PJP, coarse reticular nodular pattern

Frontal CXR in a 35 yr old male demonstrating atypical PJP with a coarse bilateral reticular pattern, large nodules and multifocal airspace shadowing.

Acute and chronic bacterial pneumonias can present with similar patterns including cavitatory lung nodules (Figure 1.6) (4,7) . Multiple lung nodules and diffuse reticulation can represent fungal disease (cryptoccocal , histoplasmosis in endemic areas),TB and septic emboli.



Figure 1.6 Bacterial pneumonia

Frontal CXR in a 40 yr old male demonstrating necrotising Klebsiella pneumonia involving the right upper lobe and left lower lobe especially at its apex.

Patients with CD4 <100cells/mm^3 present with bacterial pneumonias, atypical appearances of TB, PJP, *Mycobacterium Avium Complex* (MAC), *Cytomegalovirus* (CMV) and fungal infections. At depleted CD4 counts (typically <100cells/m^3) the commonest pulmonary fungal infection in patients with AIDS is cryptococcal pneumonia. It may also be associated with meningitis and demonstrates diffuse reticular/nodular patterns resembling PJP on CXR. Multifocal consolidation and nodules that tend to cavitate also occur with this pathogen (3, 7). Miliary and endobronchial TB give rise to non specific diffuse bilateral parenchymal patterns, while MAC encountered with CD4 < 50cellsmm will demonstrate nodules combined with airspace shadowing and cavitating opacities that can mimic TB (4). CMV encountered at CD4 <100cells/mm^3 shows perihilar and varied lower zone non-specific infiltrates often attributed to PJP (Figure 1.7) (3). This highlights the large degree to which CXR findings in patients with low CD4 counts overlap (Figure 1.8A and B).

In patients with AIDS, therefore, one or more of the differing patterns seen on CXR could be due to a number of causative organsms .These include PJP, TB,MAC, cryptocccal pneumonia, Aspergillus, and CMV. A normal CXR does not exclude active disease in severely immunocompromised patients who are unable to mount a significant inflammatory response. Non infectious AIDS related diseases such as Kaposi's sarcoma, lymphocytic interstitial pneumonitis (LIP) , non specific pneumonitis and lymphoma may all give rise to the above patterns requiring them to be included in the differential diagnosis (1, 3).

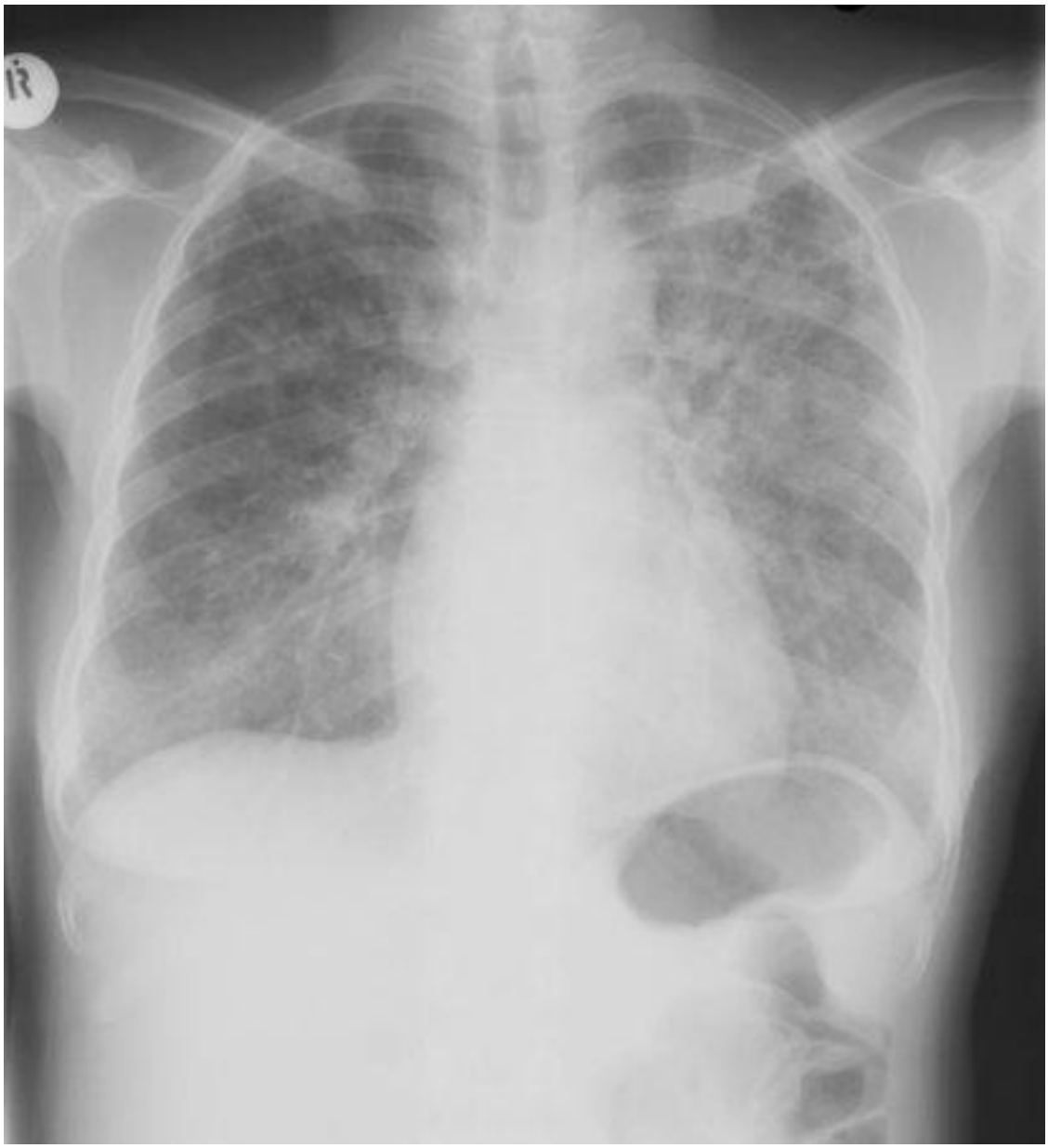
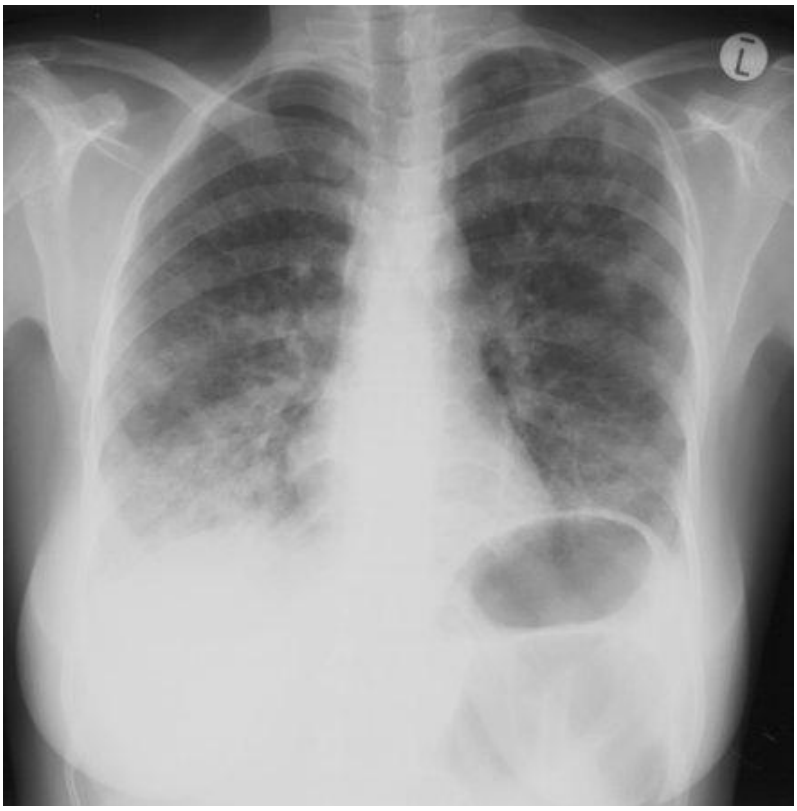


Figure 1.7 PJP and CMV

Frontal CXR in a 43 yr old woman with both PJP and CMV infections. A diffuse ground glass, bilateral reticular nodular pattern is present, with cavitation in the left apex.

Fig 1.8A below is of a frontal CXR in a 29 yr old female demonstrating atypical PJP with right lower lobe consolidation and a coarse bilateral reticular pattern.This is shown alongside Fig 1.8B of TB for comparison.The CXR features of atypical PJP are non specific and indistinguishable from those of TB.



A



B

Figure 1.8 Atypical PJP compared to TB

1.6 Pneumocystis Pneumonia

1.6.1 PJP in the Developed World

1.6.1.1 PJP detection in the Laboratory

Pneumocystis carinni was identified in 1909 as a protozoan and was found to be the causative agent for Pneumocystis pneumonia. It was reclassified as a fungus in 1988, and the infecting and host specific agent in human beings was also renamed as *Pneumocystis jirovecii* (PJP) (4,22). PJP has unique tropism for the lung, only invading and causing disseminated disease in cases of severe immunosuppression. Person-to-person transmission, rather than reactivation of latent infection when the immune system fails, is thought to be the mode of infection (22).The organism is identified by immunoflourescent staining of both its trophic and cystic forms, in sputum and BAL fluid. Earlier stains were only able to pick up either form of the pneumocystis , trophic or cystic, rather than both (22). In the absence of pneumonia, pneumocystis organsms are rarely detected by commonly employed staining methods. When cysts are visualised microscopically however, then active pulmonary disease is likely (23).

Even more sensitive is newer nested polymerase chain reaction (PCR) detection of DNA of PJP in asymptomatic individuals who do not demonstrate pulmonary disease and who may act as a reservoir of PJP disease. This may be a clinically unrecognized element in transmission (24).

1.6.1.2 Clinical History of PJP infection

The first cases of PJP were described in premature infants and malnourished children in crowded institutions in Second World War Europe, and later seen as sporadic pneumonias in immunocompromsed patients with underlying malignancies, congenital defects,

immunosuppressive therapy and in those with renal transplant (2, 25) . In the early 1980's PJP was transformed from a rare to more common pneumonia as it heralded the AIDS-epidemic(2). It became the AIDS-defining illness in two third of patients in the USA (2). In the developed world, before 1996, PJP was predominantly seen in male homosexuals. After 1996, an increasing number of heterosexual men and women presented with PJP. In HIV carriers, in the post- HAART period, well over half of them never knew their HIV status, and the onset of PJP was the first time they had learned of their HIV status (18). The first important decline in PJP prevalence occurred with Pneumocystis pneumonia prophylaxis in 1989 (25). Thereafter the emergence of HAART changed the natural history of HIV infection, causing a further significant decrease in opportunistic infection prevalence, including a decrease in OI's for which no specific prophylaxis was available (2,15) . An incidence of PJP of 20 cases /100 person years was found in the pre-HAART era in patients with CD4 counts<200cells / mm^3 compared to a rate of 0.3 cases/100 person years as early as 1998 due to HAART (1). Immune reconstitution conferred by HAART has allowed discontinuation of PJP prophylaxis when CD4 counts rise above 200 cells /mm^3. Similarly, with the use of HAART, AIDS- related deaths have dropped precipitously (15) .

1.6.1.3 The Significance of PJP as an Opportunistic Infection in the HAART Era

PJP remains the most serious and major OI in HIV infected persons despite HAART and remains a leading factor in the morbidity and mortality of patients with HIV (2, 18). Primary prophylaxis is instituted in patients with CD4 counts < 200 cells/mm^3 or in patients with oropharyngeal candidiasis regardless of the CD4 count. Secondary prophylaxis is given to patients with a history of previous PJP infection. In both instances, prophylaxis is continued for 3 months after the CD4 count rises above 200 cells/mm^3 in

response to ART (19). In a recent report, experience in a single developed world centre over a 21 year period, cites significant mortality rates due to PJP in the HAART - corticosteroid therapy period (ranging from 8,2% to 11,5%) similar to the pre-HAART , pre-corticosteroid period (18). Higher mortality rates of between 30% - 60% are also reported (26). PJP related mortality is associated with patients who have low partial pressures of oxygen, low haemoglobin, a second or third episode of PCP, and/or the need for ICU admission (18). It is the commonest cause of respiratory failure in HIV individuals, with a mortality of 80% in those patients requiring mechanical ventilation (20). In one study in 2008, two- thirds of patients were not on PJP prophylaxis, despite indications for it, and their outcomes, because of this, were less favourable than those who were on prophylaxis (20).

Patients presenting with PJP usually have CD4 counts below 100 cells/mm^3 (2,15,18). It is clear that long term HAART and immune reconstitution leads to protection from OI's including PJP when CD4 counts rise above 200 cells/mm^3 (1) . The median CD4 count of patients in the ASD (Adult and Adolescent Spectrum of Disease) Project 2000 on HAART contracting PJP, was extremely low (29 cells/mm^3) (15) and this was also found to be the case in a similar study conducted in Europe (CD4 counts 30 cells/mm^3) (2). All patients contracting PJP,whether on HAART or not, had very low CD4 counts (50 cells/ mm^3 and less) (2,15).

In New York City, despite declining HIV patients in hospitals overall, the percentage of hospitalized HIV-infected patients who have OI's has remained stable in the HAART era. Non identification of HIV infections, poor adherence to HAART and PCP prophylaxis, the possibility of poor antimicrobial efficacy at low CD4 counts and antimicrobial resistance,

all contribute to the ongoing prevalence of PCP (6) .Consistent prescribing of HAART to patients with lowered CD4 counts has the most profound effect on survival and is needed together with adequate PJP prophylaxis , when CD4<200 cells/mm^3 occurs (18). What has changed in the developed world is that more cases of PJP result from failure to diagnose HIV infection, rather than from the inevitable progression from HIV to AIDS as was seen before the availability of antiretroviral therapy (18).

1.6.2 PJP in Africa

1.6.2.1 PJP Prevalence in Africa

Low PJP prevalence rates in Africa continue to be reported in studies based on sputum results (27, 28, 29). More recent studies reporting high prevalence of PJP in Africa base their prevalence rates on bronchoscopic findings. Patients are generally referred for bronchoscopy because both clinical and radiological parameters are indeterminate (or even normal) (2, 26). At times, as in studies from Zimbabwe and Ethiopia, patients were included when they were smear negative for TB and unresponsive to anti-microbial therapy (30, 31).

The prevalence of PJP in Africa varies according to different reports and PJP co- exists with the burden of TB and bacterial pneumonias. The latter two are reportedly the dominant OI's in Africa (2). Early studies from Africa in the 1990's cited PJP as an uncommon OI with prevalence rates of 0-11% (2, 30) . Reasons for this may have been limited diagnostic resources such as laboratory and bronchoscopy facilities. The possibility of actual infection being less common may also have been due to bacterial pneumonia and tuberculosis causing early demise of the patients before CD4 count was low enough for them to contract PJP (2). Over time, studies have emerged showing a greater prevalence of

PJP in African countries. Reports from 1990 to 1995 originating in Zimbabwe where bronchoscopy was employed for diagnosis yielded higher incidence (22%) (32) and prevalence (33%)(31) for PJP, and a co-infection of 9,3% where 6 patients had both PJP and TB. A study from Kenya in 2003 found a prevalence of 37, 2% for PJP in patients who underwent bronchoscopy (33). An Ethiopian study found 30,3% prevalence of PJP (by sputum analysis) in 119 HIV positive patients who were smear- negative and culture negative for *Mycobacterium tuberculosis* (30). In another more recent Ethiopian publication, 131 smear-negative, HIV positive patients, had CXR's assessed by two radiologists blinded to the clinical diagnosis. Thirty six percent of the infections mimicked each other on CXR, where 82% of clinical diagnoses were made up of TB, PJP and Bacterial pneumonias (34). Against the more recent trend of an increased prevalence of PJP in Africa, a study from northern Tanzania using BAL in 120 HIV infected patients demonstrated a 7,5% prevalence of PJP, where median CD4 count of the patients was 47 cells/mm ^{3} (35).

PJP has had a significant unproven prevalence. In 1999, Mahomed et al published a prevalence of bronchoscopically proven PJP in 67 HIV positive patients in Johannesburg teaching hospitals, of 27,3% (in African) and 58,8% (in European) patients. Sputa were negative for TB and PJP. There was no statistical significant difference of PJP prevalence between the two HIV population groups, nor any significant difference of PJP prevalence between 67 HIV positive patients and 36 HIV negative renal transplant patients in this study (36).

A South African study in 2001 examined 39 HIV positive patients with dual *Mycobacterium tuberculosis* and *Pneumocytis jirovecii* by sputum analysis. The mean CD4

count of these patients was 90 cells/mm^3 . CXR findings included patchy bilateral infiltrates and a reticular nodular pattern, lymphadenopathy, focal consolidation with or without cavitation, and pleural effusions. Dual infection for PCP and TB as described in this paper, is only rarely reported . TB exerted the more dominant role in the morbidity of the disease. This was evident as patients who were treated for TB only, did better than those who were treated for PCP only (23).

1.6.2.2. Pneumcystis Pneumonia on CXR

Radiographically, PJP typically presents with characteristic diffuse bilateral fine reticular and hazy ground glass opacities in a over 80% of cases. However 10 – 15% may present with a normal CXR (26). Atypical features include asymmetric and nodular opacities, lobular pneumonia, cavities, lymphadenopathy and effusions (16, 26), Patients who are smear- negative for TB, and whose CXRs are either suspicious for TB or diagnostically non specific, are often treated for TB. A previous lack of awareness for PJP suggests that PJP has been a poorly recognized differential diagnosis of TB. Furthermore, radiologists may not agree with each other with regard to the radiological diagnosis. An Ethiopian study of HIV patients which yielded 33,6% with bacterial pneumonias, 29,8% with PJP, 23,7% with TB and 13% with double infection showed discordant results of 'blind' CXR readings by 2 radiologists which were highest for the diagnosis of TB and PJP (8).

It is unclear whether lack of awareness and restriction of diagnostic resources prevented accurate diagnosis of PJP in Africa, or whether indeed PJP is only now emerging as a new and serious opportunistic pathogen in Africa (2). The literature also suggests PJP has been incorrectly managed and treated under the 'guise' of smear negative TB (2, 8).

1.7 Study Aims

This study aims to analyse the proportion of bronchoscopically proven PJP and rates of co-infection in HIV infected adults, where the clinical and radiographic diagnosis was indeterminate. The study also aims to correlate the bronchoscopic diagnoses with the CD4 counts and evaluate the radiographic features.

CHAPTER TWO

MATERIALS AND METHODS

2 MATERIALS AND METHODS

Ethics approval for this retrospective study was obtained (Appendix A). HIV positive adult patients with indeterminate CXR's were collected consecutively from 1996 -2003 from the combined Radiological-Clinical Respiratory meeting taking place weekly at Helen Joseph Hospital (HJH).

The Medicine department at the hospital offers both outpatient and inpatient services, with admission occurring through casualty or through the outpatient departments, including the large HIV Clinic. The hospital has 575 beds, which includes 335 Medical beds, comprising 4 Medical Units.

The Medical Units assess and refer patients to the Respiratory Unit if they have

i) an indeterminate clinical and radiological diagnosis
ii) complicating pathology
iii) unresolving pathology
iv) the need for Cardio-thoracic intervention
v) specialised Respiratory and /or Chronic Respiratory disease eg Asmtha,

2.1 Inclusion criteria

The following inclusion criteria applied to the study:

i) HIV positive adults referred to the Respiratory Unit at HJH.
ii) Inconclusive CXRs presented at the combined Radiological-Clinical Respiratory meetings between 1996 -2003.
iii) Patients with an indeterminate clinical diagnosis, whether by clinical examination, blood results or non-contributory sputa results.
iv) Patients who underwent bronchscopy.

2.2 Exclusion criteria

The following exclusion criteria applied

Patients whose bronchoscopic results were obtained but whose CXRs were missing.

2.3 Data collection

The following data related to the patients were recorded from clinical records

i) Age , Gender

ii) Gender

iii) CD4 count

iv) Bronchoscopic result

.

2.4 Bronchoscopic tissue analysis

Tissue sections were stained with Grocott (for Pneumocystis and other fungi), alcian-blue (for Cryptococcus), Ziehl-Neelsen (ZN) (for Mycobacteria) in addition to haematoxylin and eosin. Tissue analysis was performed by the National Health Laboratory Services supporting the Helen Joseph Hospital (Professor Gil Murray).

2.5 CXR reading

The CXR's were analysed by two departmental radiologists other than the author who were blind to the bronchoscopic results, radiological reports and clinical findings other than the HIV positive status of the patients. The radiological description of the pathology found on CXR, and the patterns identified, were documented on a Data Collection Sheet (Appendix B) which included the following sections:

Location

Distribution

Description

Character:

Complications/further signs.

Radiological diagnosis

2.6 Data analysis

The proportion of PJP and TB in this group of indeterminate CXR's was determined and the presence of co-infections with PJP was evaluated.

Overall CD4 counts of all patients were assessed and CD4 counts of PJP group and of the TB group were analysed.

Sensitivity and Specificity of the CXR for the diagnosis of PJP against proven bronchoscopic result was calculated.

CXR features of proven PJP cases were analysed with regard to the the frequency of occurrence.

CXR findings in PJP were categorised into 'typical' and 'atypical' patterns.

According to Waite et al and Webb et al typical PJP CXR pattern was defined as diffuse, bilateral and perhilar, fine reticular patterns without effusions or adenopathy (4,26).

Atypical radiographic findings of PJP were defined as focal consolidation, masses, cavitation and adenopathy (4, 26).

CXR features in proven TB patients were also analysed for the frequency of occurrence.

PJP and TB CXR features were compared with regard to frequency of occurence.

Inter-reader correlation for CXR variables and diagnosis was performed.

2.7 Statistical analysis

Data was analysed using STATISTICA 9.0 statistical program. Results were expressed as mean and standard deviation or median [range] for age, CD4 counts, and frequencies and percentages for categorical variables.

Sensitivities and Specificities were calculated for CXR diagnosis vs Bronchoscopic results.

'p' values were obtained using the Fisher Exact test to look at differences in CXR signs between PJP and TB, and using the Kruskal – Wallis test for CD4 count medians.

Agreement kappa tests were used for inter-reader correlation of CXR variables and diagnoses categorised as follows:

Very good agreement kappa 0, 8 – 1

Good agreement kappa 0, 61 – 0, 8

Moderate agreement kappa 0, 41 – 0, 6

Fair agreement kappa 0, 21 – 0, 4

Poor agreement kappa < 0, 2

CHAPTER THREE

RESULTS

3 RESULTS

Ninety two patients were included in the study. The mean age was 35,1 yrs (range of 18-62yr). There were 21 patients with bronchoscopically proven PJP and 25 with bronchoscopically proven TB. The mean age of PJP patients was 34,4yrs and that of the TB patients was 33,4 yrs. Females comprised 58,1% of 92 patients and 52,3% of 21 patients with PJP.

3.1 Bronchoscopic diagnoses of 92 patients are summarised in table 3.1

Table 3.1: Diagnoses at bronchoscopy

Diagnosis*	**Patients**
Pneumocystis pneumonia	21 (22,8%)
Tuberculosis	25 (27,1%)
Non Diagnostic	13 (14,1%)
Lymphocytic interstitial pneumonia	9 (9,8%)
Nonspecific interstitial pneumonia	8 (8,7%)
Bacterial pneumonia	6 (6,5%)
Normal bronchial tissue	5 (5,4%)
Cytomegalovirus pneumonia	4 (4,3%)
Candidiasis	3 (3,2%)
Sarcoidosis	3 (3,2%)
Aspergillosis	1 (1,08%)
Bilharzia	1 (1,08%)
Lymphoma	1 (1,08%)
	100 diagnoses in 92 patients (accounting for co-infections)

*sometimes multiple

3.2 Co-infections

1 patient had PJP and TB (counted twice under diagnoses)

3 patients had both PJP and CMV

1 patient had TB and Bilharzia and LIP

1 patient had TB and Aspergillosis

3.3 Proportion of PJP

- The proportion of bronchoscopically proven PJP in 79 diagnostic samples (since 13 samples were non diagnostic) was 26,6%
- Co infection with PJP was 4/21 19%.
- The proportion of bronchoscopically proven TB was 31,6 %. The remainder constituted 41, 8% of which LIP (11,3%) , NSIP (10,1%) and bacterial pneumonias (7,5%) were the larger groups.
- Bacterial pneumonias were comprised of 3 klebsiella pneumonias, 2 staphylococcal pneumonias and 1 *Haemophilus influenzae* pneumonia

3.4 CD4 counts

54 patients out of 92 patients had CD4 counts available.

10 out of 21 PJP patients had CD4 counts available

18 out of 24 TB patients had CD4 counts available.

The available CD4 counts of the overall group, PJP subgroup and TB subgroup are summarised in Table 3.2.

Table 3.2 CD4 counts in the total sample and according to subgroups PJP and TB

	All patients	PJP	TB
CD4 counts mean	153,7 (SD=188,5)	73,7 (SD=150,7)	204,6 (SD=193,7)
Median (range)	101 (4 – 890)	13 (4 – 481)	125,5 (4 - 690)

Mean CD4 count of the PJP group was the lowest (73,7 cells/mm^3). A significant difference of median CD4 counts between the PJP and TB and other patients groups exists (p = 0, 0089) with the PJP median (13 cells/ mm^3) being the lowest. In all three groups the median CD4 counts were < 150.

3.5 Sensitivity and specificity of CXR diagnosis vs bronchoscopy

Reader 1 and Reader 2 had both an overall diagnostic sensitivity For PJP of 33% and a specificity 100%. Reader 1 and Reader 2 had the same sensitivites and specificities for the diagnosis of PJP, however , the true positive diagnosed on CXR differed between Reader 1 and Reader 2. These results are summarised in tables 3.3 and 3.4 below.

Table 3.3 Reader 1 CXR diagnosis versus bronchoscopic diagnosis for PJP

		Bronchoscopy result	
		Positive	Negative
CXR diagnosis Reader 1	Positive	7	0
	Negative	14	71

Table 3.4 Reader 2 CXR diagnosis versus bronchoscopic diagnosis for PJP

		Bronchoscopy result	
		Positive	Negative
CXR diagnosis Reader 2	Positive	7	0
	Negative	14	71

Reader 1 had a Sensitivity of 69% and Specificity of 55% for the CXR diagnosis of TB. Reader 2 had a Sensitivity 70% and a Specificity 62% for the CXR diagnosis of TB. These results are summarised in tables 3.5 and 3.6 below.

Table 3.5 Reader 1 CXR diagnosis versus bronchoscopic diagnosis for TB

		Bronchoscopy result	
		Positive	Negative
CXR diagnosis Reader 1	Positive	18	30
	Negative	8	36

Table 3.6 Reader 2 CXR diagnosis versus bronchoscopic diagnosis for TB

		Bronchoscopy result	
		Positive	Negative
CXR diagnosis Reader 2	Positive	19	25
	Negative	8	40

3.6 CXR features and patterns of PJP and TB

The frequency of the following CXR variables was similar for PJP and TB:

Bilateral, multilobar and diffuse disease, bronchopneumonia , nodules and cavitation.

Cavitation was seen in 20% of 21 PJP cases and 20% - 52% of 25 TB cases, bronchopneumonia in 40- 60% of PJP and TB cases; nodules, diffuse, bilateral and multilobar disease were seen in over 70% of PJP cases and in 40 – 60% of TB cases.

The frequency of the following CXR variables differed between PJP and TB:

Effusions were absent in all PJP cases and were present in up to 20% of TB cases.

Coarse reticulation was seen mainly in PJP (3 – 9 cases) and in 1 case of TB.

Lymphadenopathy was rarely reported in PJP (no cases by reader 1 and 2 cases by reader 2) and is reported in 5 – 8 of TB cases.

Lobar, focal, unilobar and unilateral variables are variables seen with greater frequency in TB.

The above findings are detailed in table 3.7 and figures 3.1 to 3.5 below.

Table 3.7 CXR variables of PJP patients and TB patients for both readers.

CXR Variables	PJP Reader 1	PJP Reader 2	TB Reader 1	TB Reader 2
Bilateral	19	19	12	10
Unilateral	2	2	11	13
Multilobar	19	16	15	12
Unilobar	2	2	8	11
Diffuse	19	18	12	16
Focal	1	1	2	4
Bronchopneumonia	13	9	15	10
Lobar	0	5	4	8
Nodules	15	3	10	7
Fine	4	1	1	0
Coarse	9	3	1	1
Effusions	0	0	4	5
Cavitation	5	4	6	13
Lymphadenopathy	0	2	5	8
Pneumothorax	2	0	1	1

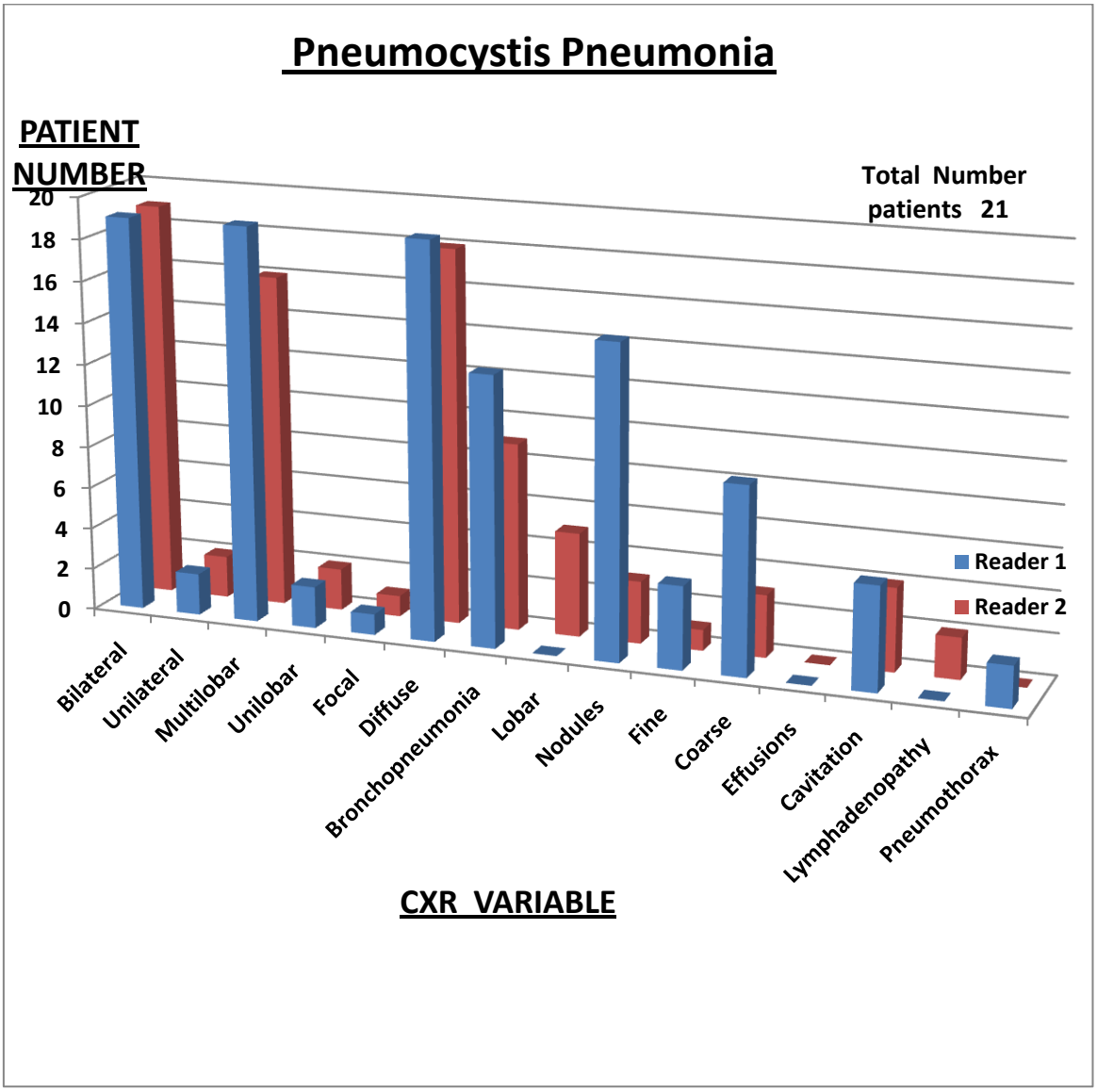


Figure 3.1 CXR features of bronchoscopically proven PJP for both readers

Figure 3.1 shows the most common radiological features of PJP are bilateral, multilobar and diffuse patterns , which are also further detailed by bronchopneumonic consolidation, nodules, coarse reticulation and cavities (in a smaller percentages). Smaller numbers are reported with fine reticular patterns. There is absence of effusions in all 21 CXR's. Two cases only (reported by one reader) had lymphadenopathy. Small numbers have pneumothorax.

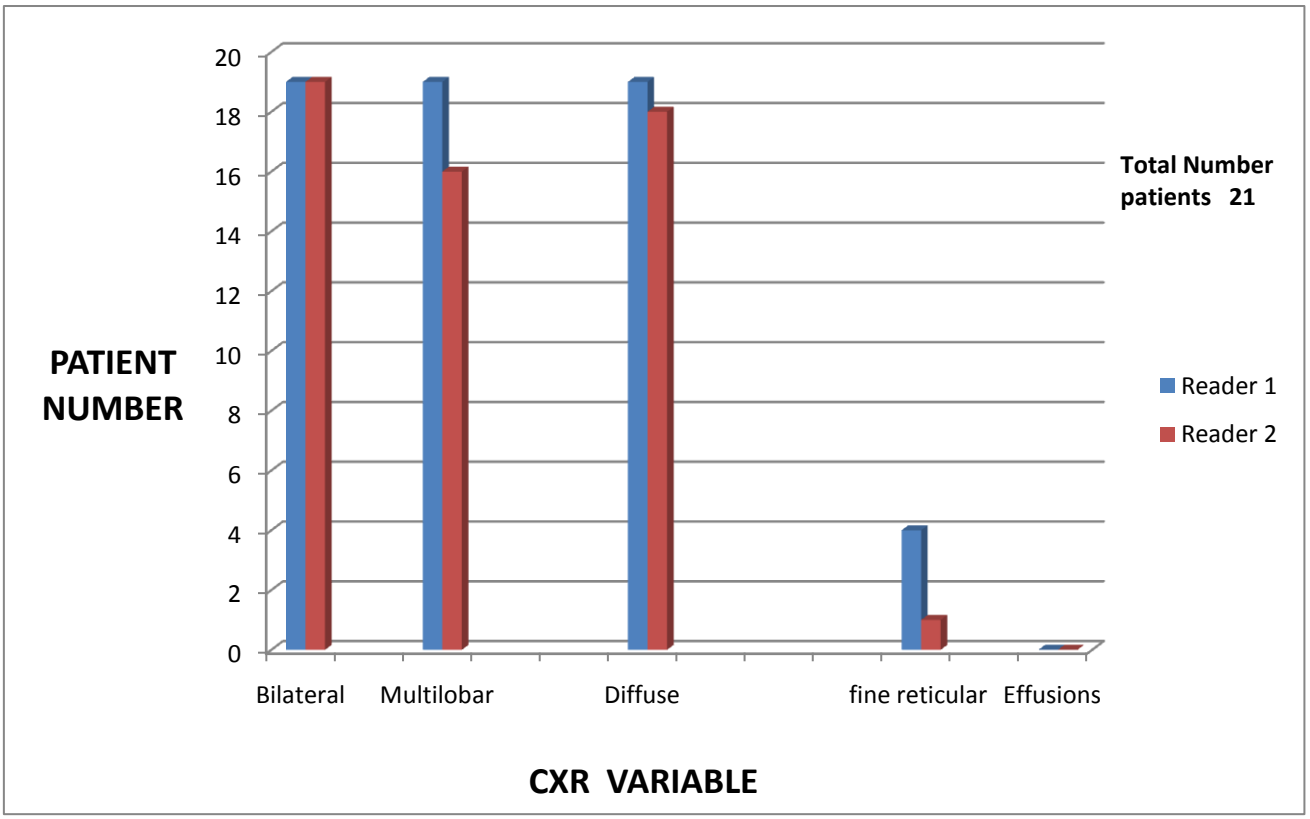


Figure 3.2 Frequencies of 'typical' CXR signs of PJP

Frequencies of 'typical' CXR signs of PJP according to typical patterns described by Waite et al and Webb et al (4,26).

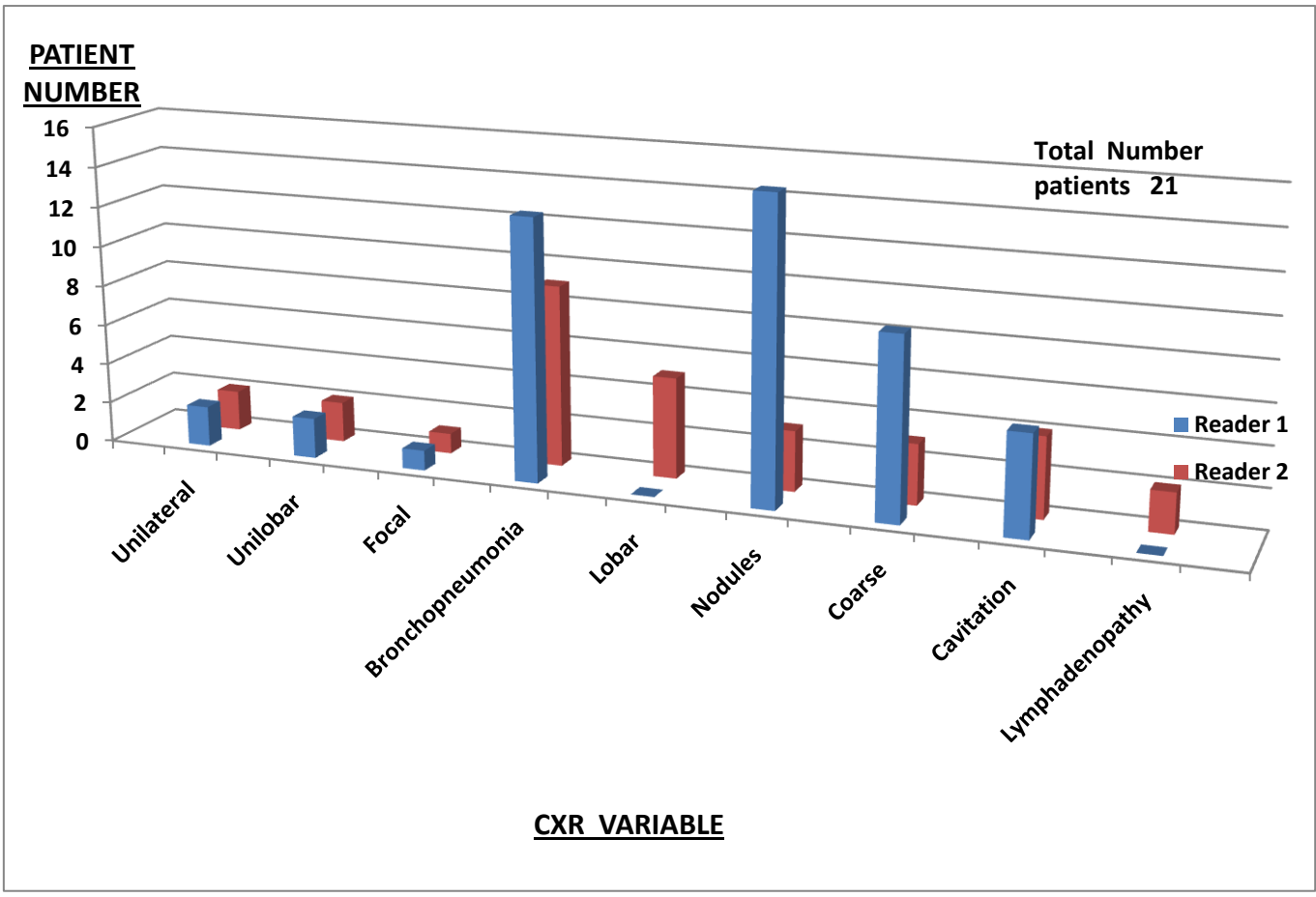


Figure 3.3 Frequency of atypical radiological signs of PJP

Frequency of 'atypical' radiological signs of PJP according to Waite et al and Webb et al (4, 26).

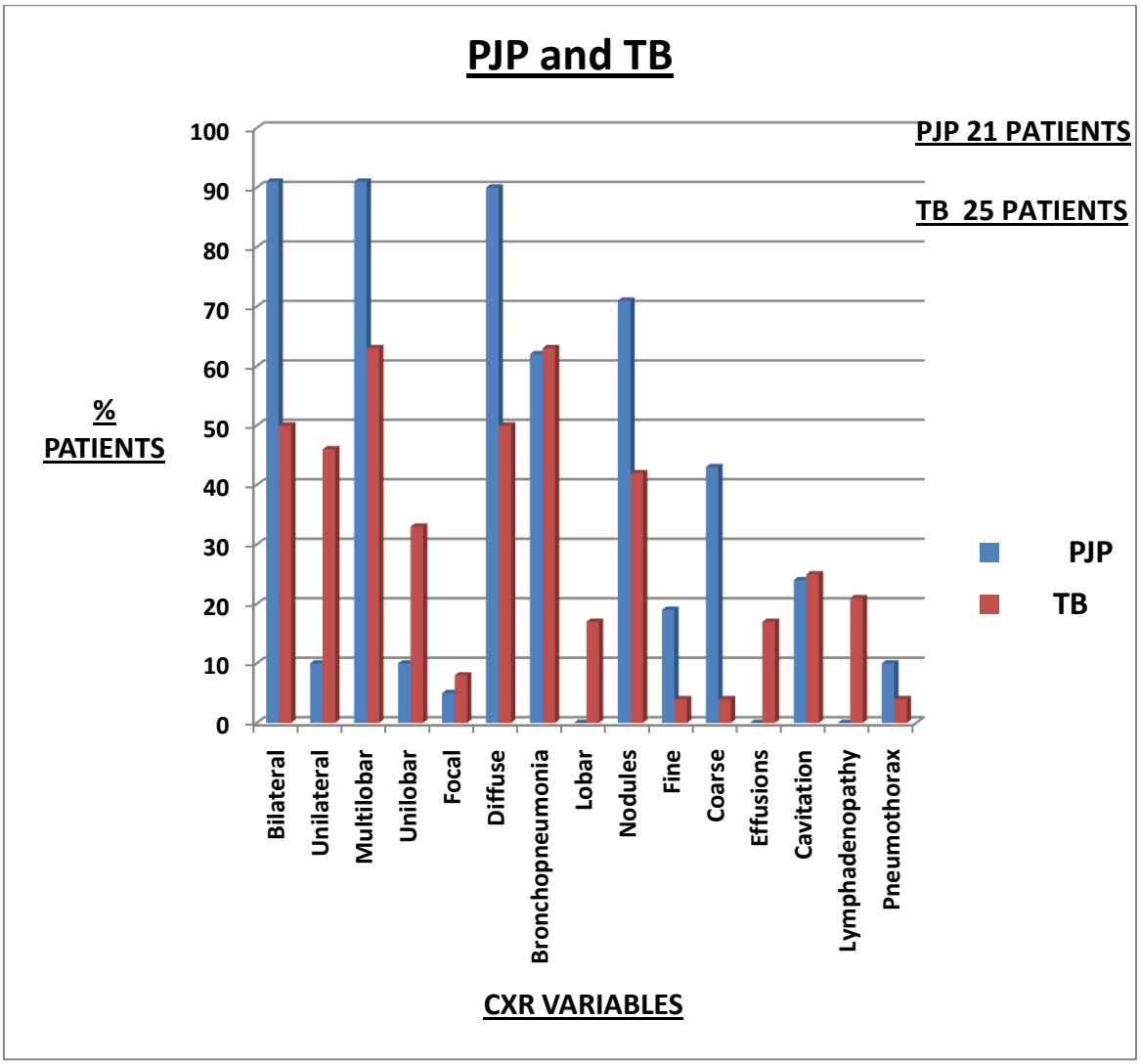


Figure 3.4 Comparison of CXR features of bronchoscopically proven PJP and TB for reader 1

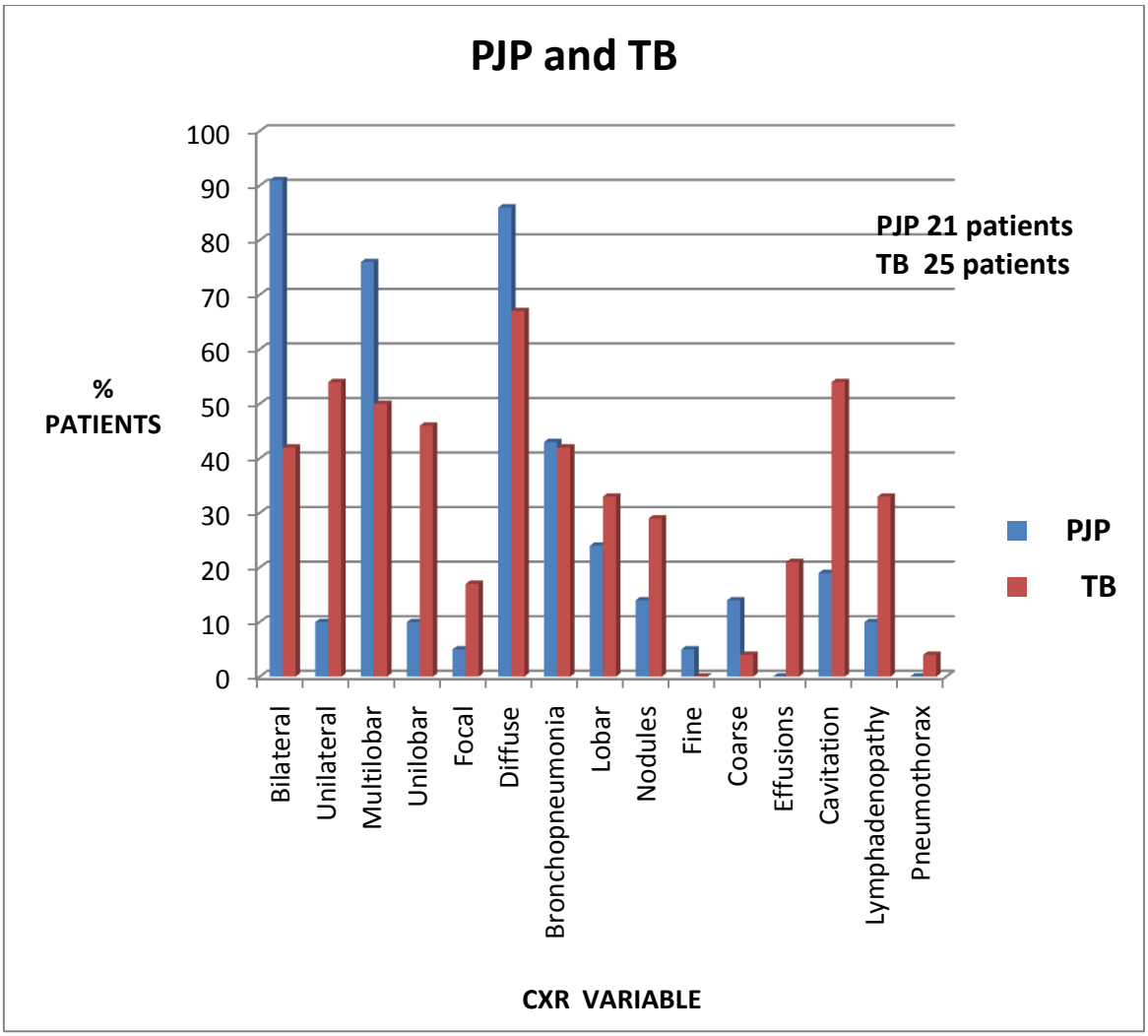


Figure 3.5 Comparison of CXR features of bronchoscopically proven PJP and TB for reader 2.

3.7 Statistical differences of radiological variables between PJP and TB

Reader 1 comparison PJP with TB		**Reader 2 comparison PJP with TB**	
Unilateral vs Bilateral disease	**p = 0.014**	Unilateral vs Bilateral disease	**p =0.003**
Unilobar vs Multilobar disease	p = 0.27	Unilobar vs Multilobar disease	**p = 0,03**
Focal vs Diffuse disease	p= 0.55	Focal vs Diffuse disease	p = 0.34
Lobar vs Bronchopneumonic	p= 0.13	Lobar vs Bronchopneumonic	p = 0.89
Fine vs Coarse Reticulation	p= 1.00	Fine vs Coarse reticulation	p = 1, 00

'p' values of significant difference were present for Unilateral vs Bilateral disease in TB vs PJP in both readers, and for Unilobar vs multilobar in TB vs PJP for reader 2.

3.8 Inter Reader Agreement Test

No CXR variables were agreed upon in the range of ‘very good’.

There was ‘good agreement’ for the presence of effusions (kappa 0,68) and location of unilateral versus bilateral (kappa 0,63).

There was ‘moderate agreement’ for unilobar versus multilobar distribution (kappa 0,56) cavitation (kappa 0,53), nodules (kappa 0,43) and inter-reader diagnosis (kappa 0,40)

‘Fair’ agreement only was found between the variables of consolidation (kappa 0,35) reticulation (kappa 0,29) and description of focal versus diffuse disease (kappa 0,21).

There was ‘poor’ agreement between readers for lymphadenopathy,

‘No agreement’ took place between readers for cardiomegaly, bullous formation, pulmonary arterial hypertension and pneumothorax, as there were not enough patients reported with these variables.

CHAPTER FOUR

DISCUSSION

4 DISCUSSION

Proportion of PJP

It is important to keep in mind that the sample population in this paper is a group of HIV patients not on ARV therapy, who had an indeterminate clinical and radiological diagnosis which led to bronchoscopy. The proportion that has been determined therefore does not represent the HIV population of the clinic, city or country. The proportion of 26.6% of PJP in our study, contrasts with the low prevalence reported in the early 1990's in Africa (up to 11%) (2, 29), but compares well with more recent reports from Zimbabwe (33%) in 1995 (31), Ethiopia (30, 3%) in 2003(30), and 37,2% from Kenya in the same year (33) . In 1999 Mahomed et al reported a PJP prevalence of 27% in HIV patients undergoing bronchoscopy in South Africa (36) which correlates well with our bronchoscopic findings. Co-infections affecting HIV infected patients confound diagnosis and classification of patients in research studies and range from 3.1% – 70% % (29, 30). Three of our patients with PJP had co-infection with CMV and 1 had co-infection with TB (19%).

Level of immune suppression based on CD4 count

Only 59% of our sample population and just under 50% of our PJP group had available CD4 counts. The mean overall CD4 count was 153 cells /mm^3 (median 100) and that the PJP group had mean CD4 which was much lower at 73 cells / mm^3 (median 13; p=0,0089). A study undertaken in South Africa in 2001 highlighted the non-specificity of chest radiographs in HIV infected patients with low CD4 counts and the difficulty in differentiating the different types of infection on chest radiographs. It is reported that as CD4 counts drop below 200 cells / mm^3, the non-specificity of chest radiographs increases (23). This forms the basis for our study sample and it probably also contributes to the low

prevalence rates of PJP reported in Africa when bronchoscopic diagnosis was not employed.

Diagnosis of PJP

Our readers demonstrated excellent specificity for the overall diagnosis of PJP (100%) but a low sensitivity (33%) as opposed to the diagnosis of TB (sensitivity 70%). This suggests that when a diagnostic decision is made based on positive CXR features, unless the findings are very suggestive of PJP, a diagnosis of TB is made instead. This may be due to increased awareness, a high index of suspicion and probably better training regarding the diagnostic features of TB. The observation of a lower specificity for the overall diagnosis of TB on CXR (55% and 62%) confirms that the diagnosis of TB is overcalled to a greater degree than PJP, and that other diagnoses, such as PJP, are probably lost and not considered in the differential diagnosis. This is especially likely to occur during an era of HIV where 50% of TB cases are known to be smear negative (37).That is, patients with negative sputa results may be diagnosed with pulmonary TB in cases where bronchoscopy would yield a different diagnosis. New sputum nucleic acid amplification testing is emerging which will more accurately identify those patients with TB (98% of patients with smear- positive and culture- positive disease) and will include identification of greater than 70% of patients with smear-negative and culture positive disease (37).

CXR Findings

A clear radiographic profile of PJP is evident from our results. PJP usually demonstrates bilateral, multilobar or diffuse disease. Coarse reticulation was far more common than the typical description of a fine reticular lacework pattern (seen in only 4 of our patients) reported in the literature. Bronchopneumonic and nodular patterns as well as cavitation,

were not typical CXR features of PJP and these overlapped with the CXR features reported in TB. This in part explains the low sensitivity of overall diagnosis of PJP. Importantly, differentiating it from TB, are the lack of effusions and lack of lymphadenopathy. Significantly, the statistical analysis identify unilateral and unilobar disease as indicators of TB rather than PJP on CXR.

In summary and in practice, for HIV patients with low CD4 counts the following radiographic configuration can indicate the possibility of PJP on CXR:

- Bilateral disease
- Multifocal disease
- Coarse reticular patterns
- Bronchopneumonic consolidation
- No effusions
- No lymphadenopathy

The following CXR signs are more likely to indicate TB :

- Unilateral disease
- Unilobar disease
- Focal consolidation
- Effusions
- Lymphadenopathy

Inter-observer variability

Observers showed a good agreement (Kappa 0.63 and 0.68 respectively) for determining bilateral vs unilateral disease and the presence or absence of effusions, moderate agreement for uni vs multi-lobar disease (Kappa 0.56) and only fair agreement on the presence of bronchopneumonic consolidation (Kappa 0.35) and reticulation (Kapppa 0.29). There was poor agreement (Kapppa 0.1) for the presence of lymphadenopathy. This suggests that reliable differentiators of PJP from TB are the presence of bilateral, multilobar disease and lack of effusions.

Limitations and further studies The low patient numbers and the highly selected population are limitations of this study. The analysis was retrospective and as a result, incomplete CD4 counts were available. Complete CD4 count data together with acquiring a larger sample number of PJP patients could be done in a prospective study. Thirteen bronchoscopy results were non diagnostic and these may have included missed true positive or true negative results with regards to the diagnosis of both Pneumocystis pneumonia and TB. This is considered a limitation of the sensitivity and specificity results for both Pneumocystis pneumonia and TB in this study. Results may not be extrapolated to patients on ARV's and of interest would be a study examining the spectrum of pulmonary diseases in these patients.

CHAPTER FIVE

CONCLUSION

5 CONCLUSION

PJP makes up more than one quarter of indeterminate CXR and clinical diagnoses in HIV infected patients. Low CD4 counts (< 200 cells / mm^3) are associated with indeterminate diagnoses. Radiologists appear to be able to make a confident diagnosis in a proportion of these patients but sensitivity of diagnosis on radiographs is low, despite the increased clinical awareness of PJP in HIV positive patients. This study shows that in patients with low CD4 levels who have bilateral multifocal disease with reticular or bronchopneumonic patterns, and no effusions or lymphadenopathy, a diagnosis of PJP should be considered at least as equally important as a diagnosis of TB or other infections based on likelihood.

Appendix A: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Rubin

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M080134**
PROJECT	The spectrum of radiological appearances in bronchoscopically proven Pneumocystis pneumonia in HIV Positive Adults
INVESTIGATORS	Dr G Rubin
DEPARTMENT	School of Clinical Medicine
DATE CONSIDERED	
DECISION OF THE COMMITTEE*	Approved unconditionally Re-issue of M031016 in the name of Dr E Joseph

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor :

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Data Collection Sheet

Chest X-ray report (mark all that apply):

Location: ☐ Unilateral ☐ Right ☐ Left ☐ Bilateral
Involved lobe(s): _____

Distribution: ☐ Unilobar ☐ Multilobar
☐ Focal ☐ Diffuse ☐ Patchy

Character: ☐ **CONSOLIDATION**
☐ Lobar ☐ Segmental ☐ Bronchopneumonia

☐ **NODULAR**
☐ Smooth ☐ Irregular ☐ Large
☐ Small ☐ Miliary

☐ **RETICULAR**
☐ Fine ☐ Coarse

Complications: ☐ Cavitation
☐ Pleural effusion (location if present:)
☐ Lymphadenopathy (location if present)
☐ Pneumothorax
☐ Bullous Formation
☐ Cardiomegally
☐ Pulmonary arterial hpertension

Radiological Diagnosis (Tick the single most likely box):
☐ Normal
☐ Bacterial pneumonia
☐ TB
☐ Pneumocystis pneumonia
☐ Lymphoma
☐ Unknown Diagnosis
☐ Kaposi Sarcoma
☐ Interstitial pneumonitis
☐ Lymphocytic Interstitial pneumonitis
☐ Non specific pneumonitis
☐ Other (Please state):

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