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Pulmonary complications of HIV disease: 10 year retrospective evaluation of yields from bronchoalveolar lavage, 1983–93

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Abstract

Background **– Pulmonary disease is a major contributor to morbidity and mortality in patients with HIV infection and AIDS. The aim of this study was to describe bronchoscopic findings and the spectrum of pulmonary pathogens in HIV seropositive patients undergoing investigation of respiratory disease over a 10 year period in a major UK referral centre.**

Methods **– Recruitment was procedure based with data being captured when bronchoscopy was clinically indicated. Data were evaluated from 580 HIV seropositive patients (559 men, age 13–65 years) over a 10 year period from June 1983 to March 1993.**

Results **– A total of 947 bronchoscopies was performed. The most frequent pulmonary pathogen isolated from bronchoalveolar lavage (BAL) fluid in 44% of all bronchoscopies was *Pneumocystis carinii*. Of all patients studied, 324 (55%) had at least one cytologically confirmed episode of *P carinii* pneumonia; this was AIDS defining in 219 (38%) of patients who underwent bronchoscopy. Between 1987 and 1993 the overall diagnostic yield from BAL fluid was 76%; 25% of all bronchoscopies yielded positive microbiological results, the most frequent isolates being *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas* spp, and *Haemophilus influenzae*. Mycobacteria were identified in 8% of patients; *M tuberculosis* was the most common being identified in 3% of lavage samples and in 4% of patients. No drug-resistant *M tuberculosis* was found. Viral isolates (mainly cytomegalovirus) were identified in up to 31% of BAL fluid samples. Endobronchial Kaposi's sarcoma was seen in 15% of patients at bronchoscopy.**

Conclusions **– Of the 1956 newly diagnosed HIV seropositive patients receiving clinical care at St Mary's Hospital over this period, approximately 30% underwent bronchoscopy. Diagnostic rates for *P carinii* pneumonia, endobronchial Kaposi's sarcoma, and bacterial and mycobacterial infection have remained largely constant since 1989. Bronchoalveolar lavage produces high diagnostic yields generally, and *P carinii* pneumonia remains a common cause of pulmonary disease in these patients.**

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Keywords: HIV infection, *Pneumocystis carinii* pneumonia, bronchitis, AIDS.

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The pulmonary complications of HIV disease are now well recognised and described. Considerable uniformity in the diagnostic approach has evolved in which fibreoptic bronchoscopy, coupled with bronchoalveolar lavage (BAL), has become routine.[1–10]

During the 10 year period from January 1983 to March 1993 1956 patients with HIV disease, including 914 with AIDS, have received their regular clinical management at St Mary's Hospital, Paddington, London, a large HIV referral centre. The aim of this study was to evaluate by retrospective analysis the diagnostic yields and the spectrum of pulmonary pathogens obtained by fibreoptic bronchoscopy and BAL in HIV seropositive patients with respiratory symptoms for the 10 year period June 1983 to March 1993.

Methods

PATIENTS

Between June 1983 and the end of March 1993 580 HIV seropositive patients (559 men) aged 13–65 years underwent fibreoptic bronchoscopy for investigation of respiratory symptoms. The indications for bronchoscopy were new respiratory symptoms of several days duration (cough or breathlessness), often associated with systemic features (fever, lassitude, or weight loss), and an abnormality in pulmonary physiology (reduced carbon monoxide transfer factor) or chest radiology.

Following clinical evaluation fibreoptic bronchoscopy was performed within 48 hours except in patients considered too ill for the procedure. The decision to perform a bronchoscopy did not delay starting treatment for either *Pneumocystis carinii* pneumonia or for a bacterial pneumonia if these were thought on clinical grounds to be the most likely diagnoses.

BRONCHOSCOPY AND BRONCHOALVEOLAR LAVAGE (BAL)

Fibreoptic bronchoscopy was performed in standard fashion. Arterial oxygen saturation

was monitored and supplemental oxygen delivered as required. After segmental and subsegmental inspection to evaluate the presence of endobronchial Kaposi's sarcoma, the bronchoscope was wedged in the medial segment of the middle lobe or in the segmental bronchus corresponding to the area of maximal radiographic abnormality. Bronchoalveolar lavage was performed by instillation of up to four sequential 60 ml aliquots of sterile isotonic saline warmed to 37°C and then removed under low pressure and pooled in a 500 ml polypropylene bottle. All BAL specimens were evaluated for bacteria, fungi, and mycobacteria by conventional microbiological techniques, for viruses by cell culture and, in some cases, by immunofluorescent identification of specific viruses and for detection of cytomegalovirus by detection of early antigen fluorescent foci (DEAFF). The presence of *P carinii* was determined by Giemsa and Grocott stains on direct smears and cytospin preparations. Apart from the introduction of immunofluorescent techniques for viral identification in the last three years, there have been few changes in the diagnostic techniques employed during the period of study. In a limited number of cases, transbronchial or endobronchial biopsy was performed.

SOURCES OF DATA

Patients who underwent bronchoscopy were identified from records kept in the endoscopy suite. Demographic details including sex and date of birth, risk factors for the acquisition of HIV, date of AIDS defining diagnosis, and the AIDS defining diagnosis were obtained from patient case records and from a computerised data base. In those patients in whom endobronchial Kaposi's sarcoma was diagnosed at bronchoscopy, hospital case records were searched to evaluate the presence and date of any antecedent extrapulmonary Kaposi's sarcoma. Individual cytological, microbiological, virological, and mycobacteriological results were obtained from the respective laboratory departments and supplemented where necessary from the case notes.

TREATMENT

Throughout the study period there have been some changes in both the prophylaxis and treatment of major opportunistic infections. *P carinii* pneumonia has been treated throughout the 10 year period in our unit with high dose co-trimoxazole as first line treatment, and dapsone and trimethoprim (or more recently clindamycin and primaquine) if intolerance occurs. Short courses of high dose corticosteroids were introduced in 1990 as adjunctive therapy in patients with *P carinii* pneumonia with respiratory failure. Since 1988 secondary prophylaxis has been offered to patients (fortnightly nebulised pentamidine, thrice weekly co-trimoxazole, or thrice weekly dapsone and pyrimethamine). Since 1989 primary prophylaxis has been offered to all patients with CD4 counts of $<200/mm^3$ or with symptoms of HIV disease. CD4 counts were not available in all patients in this study and these data are not included. In 1987 patients with AIDS were offered zidovudine if clinically appropriate. Since 1987, by which time patient numbers had rapidly increased, the indications for diagnostic bronchoscopy are not considered to have changed substantially.

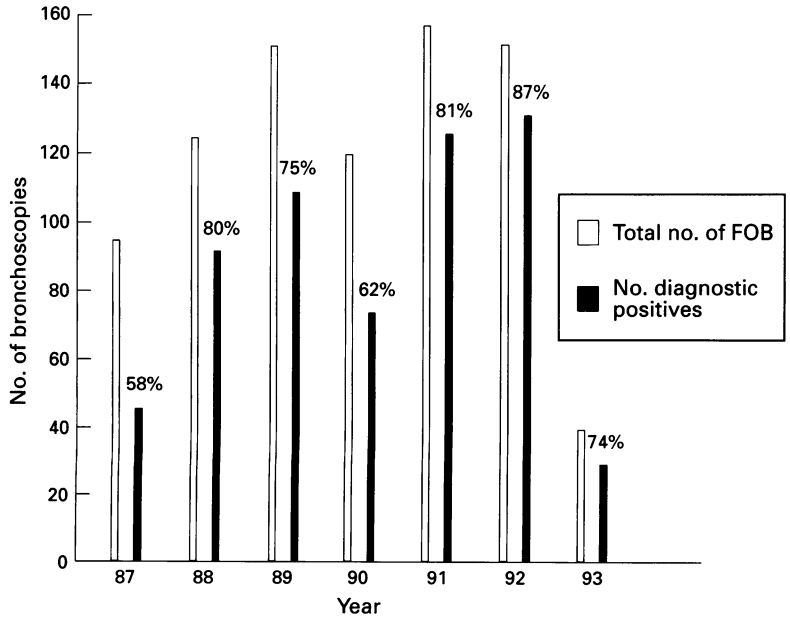

Figure 1 Total diagnostic yield from fibreoptic bronchoscopy (FOB) and bronchoalveolar lavage from January 1987 to March 1993 showing both the absolute number and the percentage of diagnostic positives.

Results

Between June 1983 and March 1993 580 patients known to be HIV seropositive underwent diagnostic bronchoscopy. Their ages ranged from 13 to 65 years and most (92%) were homosexual or bisexual men. During this period 1956 patients with HIV disease, including 914 with AIDS, have received their regular clinical management at this hospital; approximately 30% of these patients underwent bronchoscopy at some stage in their clinical course and a total of 947 bronchoscopies was performed. Of the 580 patients who had bronchoscopy, 343 had the procedure performed once, 144 twice, 65 three times, 21 on four occasions, six on five occasions, and one patient more than five times. There was a rapid increase in the number of HIV cases in 1987 at which time clinical practice was standardised. The total diagnostic yield from bronchoscopy expressed both in absolute and percentage terms from 1987 to 1993 is illustrated in fig 1. For the period 1987–93 a positive overall diagnosis was made from the results of bronchoscopy in 76% of cases, although annual rates varied between 58% and 87%. Annual yields from BAL in individual diagnostic categories are shown in fig 2. Diagnostic yield was taken as the number of bronchoscopies with a positive laboratory finding divided by the total number of bronchoscopies performed.

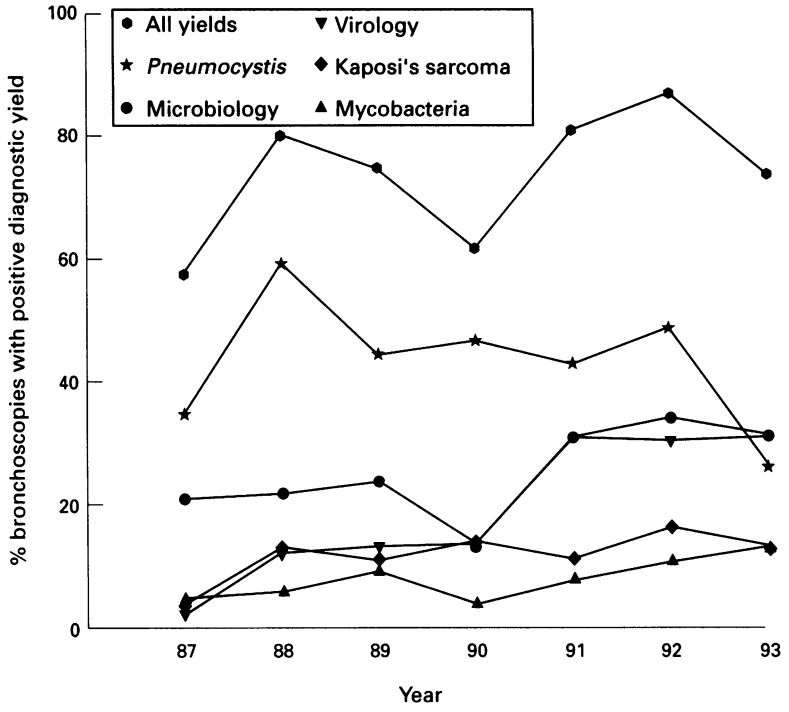

Figure 2 Annual percentage of bronchoscopies yielding positive diagnoses delineated by diagnostic category, the 1993 data relate only to the first three months.

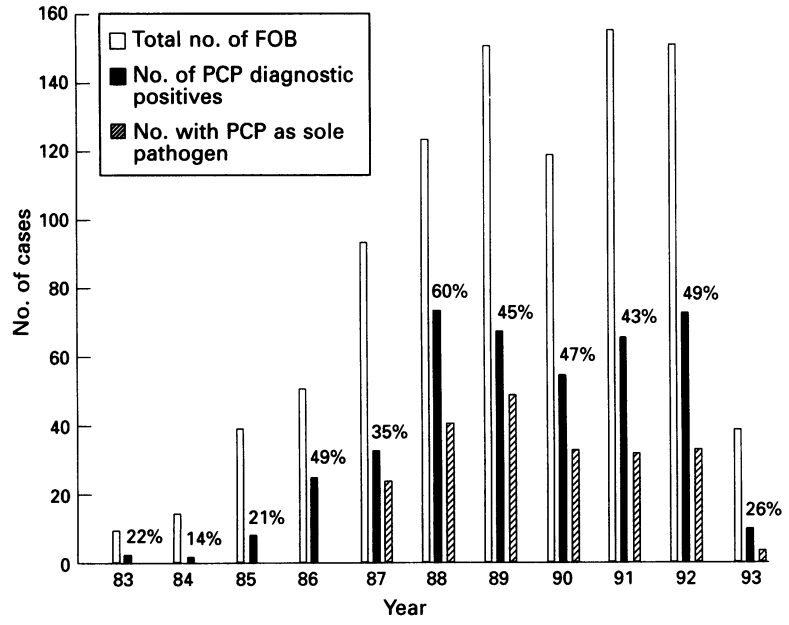

Figure 3 Diagnostic yield from fibreoptic bronchoscopies (FOB) with bronchoalveolar lavage for Pneumocystis carinii pneumonia (PCP) from June 1983 to March 1993 showing both the absolute number and the percentage of diagnostic positives. The number of bronchoscopies with Pneumocystis carinii as the sole isolated pathogen between 1983 and 1986 is not shown.

CYTOLOGY: *PNEUMOCYSTIS CARINII* PNEUMONIA

The diagnostic yield from BAL fluid (1983–93) for *P carinii* pneumonia is shown in fig 3. Of the bronchoscopies performed between 1987 and 1993 in which *P carinii* was identified in the BAL fluid (n=379), the organism was the sole pathogen in 215 (57%). Of the 591 patients studied in this series until the end of March 1993, 324 (55%) had at least one cytologically proven episode of *P carinii* pneumonia; amongst these patients this was AIDS defining in 219 (68%) cases. Seventy six patients had two or more episodes of *P carinii* pneumonia.

Of the 324 new cases of *P carinii* pneumonia diagnosed bronchoscopically between 1983 and 1993 there were 26 deaths (8%) during the acute episode (within one month of diagnosis). Between 1987 and 1993, of the 288 newly diagnosed cases of pneumocystis pneumonia during that time there have been only 13 deaths within one month of bronchoscopy (4·5%). Of these 13 patients, five had no other associated pulmonary disease diagnosed bronchoscopically. Of the remainder, two had coexistent Kaposi's sarcoma, four had associated viral pathology (two cytomegalovirus, one adenovirus, one herpes), and two had pyogenic infection with *Pseudomonas* spp, of which one also had a high grade endobronchial non-Hodgkin's lymphoma.

MICROBIOLOGY

The percentage of bronchoscopies yielding positive bacterial culture varied annually between 21% and 34% with a mean of 25%. *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas* sp, and *Haemophilus influenzae* were the organisms most commonly isolated, being found in 56 (6·7%), 42 (5·0%), 31 (3·7%), and 29 (3·5%), respectively of the 834 bronchoscopies performed between 1987 and 1993. Whether these isolates were pathogenic in all cases is uncertain. Amongst isolates of *Staph aureus* (n=56) it was the sole isolate in only 13 cases; in 29 of the remaining 43 cases it was found in association with either *P carinii* or Kaposi's sarcoma (or both).

Fungal isolates in BAL fluid were found in 83 instances of which *Candida* spp were clearly predominant (n=67) but of unlikely clinical significance. Pulmonary isolates of *Aspergillus* spp were rare (n=9), as were those of *Cryptococcus* spp (n=3). In one patient, a resident in the USA, *Histoplasma capsulatum* was isolated on two occasions.

MYCOBACTERIA

Between 1987 and 1993 mycobacteria were isolated in 63 of 834 (7·5%) samples of BAL fluid with annual prevalence rates between 5% and 13%. Of the mycobacterial pathogens isolated, *M tuberculosis* was the commonest, occurring in 23 of 834 samples of BAL fluid (2·8%) and from 22 of the 497 patients (4·4%). No drug-resistant organisms were observed amongst these isolates. Four of the patients had culture positive evidence of extrapulmonary tuberculosis.

The remaining mycobacterial isolates (n=40) were atypical non-tuberculous mycobacteria obtained from 39 lavage samples (5%) and from 36 patients (7%). Of these, *M xenopi* was most commonly isolated (in 17 patients) followed by *M avian intracellulare* in 14.

VIROLOGY

Cytomegalovirus (CMV) was the principal virus with yields from bronchoscopic examination having increased in the last three years of the study, probably as a result of improved cell culture techniques and introduction of the DEAFF test. CMV was identified overall in 132 (16%) of BAL samples. In a nested study over the period April 1989 to January 1992 detection of CMV in BAL fluid by polymerase chain reaction (PCR) was compared with standard cell culture techniques. Of the 68 samples of BAL fluid utilised for both sets of analysis, CMV was identified using PCR in 33 (49%) and by conventional analysis in nine (13%). All the latter cases were identified by PCR. Other viruses identified in BAL fluid were: adenovirus in eight, HSV in 14, parainfluenzae III in four, and influenza B in two.

ENDOBRONCHIAL KAPOSI'S SARCOMA

Endobronchial Kaposi's sarcoma was categorised as local if lesions were confined to the wall of the trachea or involved a segmental bronchus of a single lobe, or extensive if lesions involved both the tracheal wall and a segmental bronchus of a single lobe or two or more lobes. The total number of patients with bronchoscopically visualised local or extensive Kaposi's sarcoma over the period 1987–93 was 74, representing an incidence of 15%; 73 of these patients were homosexual or bisexual men. A biopsy sample was only taken if there was either clinical or histological doubt regarding the diagnosis at other more accessible sites, hence in only five cases was endobronchial Kaposi's sarcoma confirmed by biopsy and in a further two cases histological appearances were equivocal.

In 26 patients the initial unequivocal bronchoscopic appearance of Kaposi's sarcoma was evaluated as local disease, and in 48 as extensive. No records on the absence or presence of extrapulmonary Kaposi's sarcoma or its temporal relationship to pulmonary Kaposi's sarcoma were available in nine of the 74 patients. In 61 of the remaining 65 patients there was documented diagnostic evidence of preceding extrapulmonary Kaposi's sarcoma – cutaneous, visceral, lymphatic, or palatal. In the remaining four patients pulmonary Kaposi's sarcoma was AIDS defining in two, with other manifestations of the tumour appearing within one month, and in the other two patients local presentations of pulmonary Kaposi's sarcoma were the first presentation of the tumour but these were not AIDS defining.

In the 18 patients who had more than two successive bronchoscopies who had endobronchial Kaposi's sarcoma (all of whom had received chemotherapy), in only two did endobronchial Kaposi's sarcoma regress macroscopically. In the other 16 patients endobronchial lesions remained stable or progressed. Of the 101 bronchoscopies performed between 1987 and 1993 in which endobronchial Kaposi's sarcoma was unequivocally observed (representing an overall procedure incidence of 12%), it was the sole positive finding in 33 and presumably accounted exclusively for the pulmonary features in these patients at that time. In 26 of the remaining 68 procedures, and in 19 patients, Kaposi's sarcoma was associated with evidence of *P carinii* pneumonia in the BAL fluid.

ENDOBRONCHIAL/TRANSBRONCHIAL HISTOLOGY

Since 1987 transbronchial biopsies were taken in 191 of 834 (23%) bronchoscopies. There was a fall in biopsy rate over the period of study from 54% in 1987 to 7% in 1992. Most of the biopsies reinforced the diagnostic information obtained from BAL fluid and in only nine cases did they yield additional information (five cases of lymphoid interstitial pneumonia, two cases of non-Hodgkin's lymphoma, and two cases of *P carinii* pneumonia).

Discussion

This study aimed to evaluate bronchoscopic findings and diagnostic yields in HIV seropositive patients and how these may have changed with time. Unlike other studies where patient enrollment had strict inclusion criteria, recruitment to this study was procedure based, which introduces bias, yet the purpose of this study was to evaluate the clinical usefulness of bronchoscopy in this setting.[11–15] Data were captured for all patients at points in their clinical course when bronchoscopy was considered appropriate on clinical, radiographic, or physiological grounds. This approach is open to criticism as the bronchoscopic findings were not prospectively evaluated in conjunction with clinical indices of disease progression, regression, specific therapeutic intervention, or outcome but, as already stated, the aim of this study was simply to evaluate the clinical usefulness of bronchoscopy in routine clinical practice. Furthermore, a general problem with all clinical studies of diagnostic yields for *P carinii* pneumonia by bronchoscopy is the case definition. As confirmatory open lung biopsies or necroscopic examinations are rarely available, the denominator will always include unconfirmed cases that were clinically typical, responded appropriately to specific therapy, and where no alternative diagnosis emerged. A problem with this is that cases of pneumonia responsive to co-trimoxazole may include some bacterial cases.

Bearing these reservations in mind, most bronchoscopic studies previously reported[1 11–15] were conducted during the early years of the HIV epidemic and contained data on fewer patients than the present study. The larger previous studies[1 14] have shown both the high diagnostic accuracy and sensitivity and the high negative predictive value (or low false negative rate) of both BAL and transbronchial biopsy. This study confirms previous observations that *P carinii* pneumonia is still the most important pulmonary complication. Our findings also support the limited additional information obtained by transbronchial biopsy.[1–14] Finally, our overall frequency of isolation of pulmonary pathogens from BAL fluid is in line with

others[14] at 76%, although annual trends did fluctuate.

Over the last 10 years *P carinii* has been identified in respiratory tract specimens in 55% of all HIV seropositive patients undergoing bronchoscopy, providing the index AIDS defining diagnosis in 219 (38%) of these patients. For the last seven completed years (1986–93) between 35% and 60% of all bronchoscopies annually were positive for *P carinii* pneumonia (fig 3) with a mean of 47%, and over the last four years (1989–92) there has been no trend towards a decline, despite widespread use of zidovudine and prophylaxis, which confirms a similar recent observation.[16]

Bacterial infections are common in HIV infected patients.[17] In an early series, Murray *et al*[1] reported that 2·5% of patients with HIV pulmonary disorders had bacterial infection. In the current study, largely of homosexual or bisexual men containing very few intravenous drug abusers, although *Str pneumoniae* and *H influenzae* were common, it is interesting that *Staph aureus* was the most common bacterial isolate. In several studies *Staph aureus* has not been reported as a frequent cause of pneumonia[1 16–19] whereas other series have reported staphylococcal pneumonia in HIV disease in up to 8%,[20–22] often occurring in association with pulmonary Kaposi's sarcoma or *P carinii* pneumonia – observations which our data support.

Our data also suggest a trend towards an increase in bacterial yields from BAL fluid over the study period, an observation in line with that of Pitkin *et al.*[16] However, these yields may be an underestimation due to antibiotic therapy before bronchoscopy. This study emphasises that fungal infection is rare. The frequent isolation of *Candida* is almost certainly not of clinical relevance. It is interesting to note that there were only slight differences in the characteristics of fungal isolates (other than *Candida* spp) compared with the previously reported large North American series.[1 14]

A recent study identified that, in patients with AIDS in England and Wales, 4·6% also had tuberculosis.[23] During two survey periods (1983 and 1988) of tuberculosis notifications only one and nine patients, respectively, were known to be infected with HIV, suggesting that HIV infection has not yet had an appreciable impact on tuberculosis notifications. Another study[24] reported a 6% incidence of both pulmonary and extrapulmonary tuberculosis in patients with HIV infection and, in contrast to data from urban centres in the USA,[25] almost no primary drug resistance. In this study we observed a small increase in isolates of *M tuberculosis* from BAL fluid during the last 2–3 years. *M tuberculosis* was isolated in only 3% of bronchoscopies between 1987 and 1993 and in 4% of patients, emphasising that so far there is little overlap between pulmonary tuberculosis and proven seropositive HIV status in London and that, as yet, multidrug-resistant isolates of *M tuberculosis* have not occurred, in contrast to the situation with AIDS in Africa or intravenous drug users with AIDS in New York.

Current evidence suggests that CMV in the lung of patients with AIDS does not cause disease, nor does its presence adversely affect survival.[26–30] Our isolation rates of CMV from BAL fluid were low compared with other series,[1 14 26] including a small series of our own[28] in which CMV was detected in BAL fluid by PCR. This was probably due to inadequacies in cell culture techniques which, when rectified, resulted in increased viral yield.

Intrathoracic Kaposi's sarcoma may account for pulmonary disease in patients with HIV infection.[31] Whilst Kaposi's sarcoma occurs in up to 25% of all patients with AIDS,[32] the incidence of pulmonary manifestations has been variably reported at between 3% and 13% of patients with AIDS,[1 33] in up to 32% of patients with AIDS and cutaneous Kaposi's sarcoma,[33–35] and in approximately 10% of patients with AIDS and respiratory symptoms.[1 36] In two further recent clinical studies the incidence of endobronchial Kaposi's sarcoma in HIV patients was, respectively, quoted at 8%[37] and 13%[38] although, by contrast, bronchopulmonary Kaposi's sarcoma has been found at necropsy in 47% of patients with AIDS who had cutaneous manifestations of the tumour.[39]

The incidence of bronchoscopically visualised endobronchial Kaposi's sarcoma between 1987 and 1993 was 15% amongst all patients and 12% amongst all procedures, with annual rates since 1988 fluctuating between 10% and 16%. Almost all patients with endobronchial Kaposi's sarcoma had evidence of extrapulmonary disease.

The final point to address relates to trends in workload with respect to patient requirements for bronchoscopy, and the implications that this may have for future health care provision and resource planning. Our data suggest that at least 30% of all patients with HIV infection will, at some stage, need a bronchoscopy.

In conclusion, this retrospective analysis presents data from a 10 year period in patients with HIV infection who received their clinical care at a principal UK referral centre. The data reflect routine respiratory clinical practice and the findings are purely descriptive, based on routine laboratory analysis of BAL fluid obtained at bronchoscopy. Our analysis over time has allowed some observations of minor trends in the important pulmonary diagnostic categories within the spectrum of HIV infection. Such data acquisition is important in defining future health care needs, clinical care supervision, and research priorities.

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