ABC of AIDS

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AIDS AND THE LUNG

Opportunistic infections
Non-opportunistic infections
Non-infective disorders

The lungs are commonly affected in the acquired immunodeficiency syndrome (AIDS), accounting for almost half of all initial presentations. As the numbers of patients increase so will the workload for thoracic and general physicians. Pulmonary manifestations include both opportunistic and non-opportunistic infections as well as non-infective disorders. The presenting clinical features and treatment of these disorders are described below in their order of incidence. This is followed by an outline of investigation and diagnosis.

***Pneumocystis carinii* pneumonia**

Chest radiograph of patient with typical appearances of pneumocystis pneumonia.

Pneumocystis carinii pneumonia accounts for 85% of pulmonary infections in AIDS. Patients typically complain of a prolonged history (6-8 weeks) of breathlessness and dry cough, and a common symptom is that of an inability to take a deep breath. Fever is almost invariable, but the patients rarely complain of a high temperature.

Treatment is with co-trimoxazole 20 mg/kg/day (of the trimethoprim component) diluted 1/25 in either 0.9 saline or 5% dextrose. Two weeks of intravenous therapy are followed by one week of oral therapy. If oral treatment is not tolerated by the patient or if fever or symptoms recur then intravenous treatment should be resumed. Eighty per cent of patients develop some side effects, the most common of which are nausea, rashes, and cytopenia. Prophylactic prochlorperazine (dose according to patient weight) is used routinely, but despite this nausea proves intractable in some patients. Intravenous folinic acid (15 mg/day) is given to prevent cytopenia if the platelet count is below $50 \times 10^9/l$ or the white cell count below $1.5 \times 10^9/l$ either before or during treatment.

Pentamidine may be used as an alternative treatment at a dose of 4 mg/kg/day (of the isethionate salt) by intramuscular injection or diluted in 250 ml of 5% dextrose as a slow intravenous injection (over 2 hours). The major side effects are hypotension and hypoglycaemia; hence blood pressure and blood glucose concentrations need to be closely monitored. Nephrotoxicity, hepatotoxicity, and marrow depression have also been reported. Co-trimoxazole and pentamidine are equally effective when used as first line treatment, but there is no synergistic effect.

Seventy per cent of patients survive a first episode of *Pneumocystis carinii* pneumonia. The statistics show a subsequent life expectancy of 9 months (USA) and 12.5 months (UK). As knowledge about AIDS becomes more widespread patients are tending to present earlier in their disease, and these figures will undoubtedly improve. At present, however, a two year survival is uncommon.

Recurrent episodes of *Pneumocystis carinii* pneumonia have been reported in up to 20% of patients, but in our experience this is unusual. Prophylaxis can be given as co-trimoxazole (2 tablets/day) or Fansidar (pyrimethamine-sulphadoxine) one tablet weekly. The role of mechanical ventilation is discussed below.

Treatment of *Pneumocystis carinii* pneumonia

Co-trimoxazole 20 mg/kg/day
diluted 1:25 in 0.9% saline or 5%
dextrose

Pentamidine isethionate
4 mg/kg/day
intramuscularly or by slow
intravenous infusion in
250 ml 5% dextrose

Cytomegalovirus

A transbronchial biopsy specimen showing a large eosinophilic nuclear inclusion (arrowed) in a pneumocyte infected with cytomegalovirus (haematoxylin and eosin stain). (Courtesy of Dr Meryl Griffiths.)

Mycobacteria

Tissue stained with Ziehl-Neelsen technique showing red staining of mycobacteria (x 400). (Courtesy of Dr Meryl Griffiths.)

Other conditions

Bacterial pneumonia
Fungi
Kaposi's sarcoma
Lymphoid interstitial pneumonia
Alveolar proteinosis

Cytomegalovirus (CMV) can present as a pneumonic illness with cough and breathlessness in immunocompromised patients such as those undergoing bone marrow or renal transplantation. Cytomegalovirus as a sole cause for pneumonitis is, however, unusual in patients with AIDS. It is more commonly seen in conjunction with *Pneumocystis carinii* pneumonia. The presence of cytomegalovirus in patients with *Pneumocystis carinii* pneumonia does not affect the response or outcome of treatment with co-trimoxazole alone, which suggests that cytomegalovirus is not a major pathogen of the lung in AIDS. In view of this, if an effective medication were developed it would not seem to be appropriate therapy for all patients with AIDS in whom cytomegalovirus is found in the lung. One promising agent is DHPG (9 (1, 3 dihydroxy-2-propoxymethyl) guanine), which is undergoing clinical trials but which seems less effective against cytomegalovirus in the lung than in other organs. We would use this treatment in patients with respiratory symptoms in whom cytomegalovirus was the only pathogen found or in whom clinical deterioration occurs despite adequate treatment of other copathogens.

The finding of atypical mycobacteria in the lung has not been shown to reduce long term survival. In the United Kingdom *Mycobacterium xenopi* and *M. kansasii* are found more commonly than *M. avium-intracellulare*, which is widely reported in the United States of America. These infections are indolent and usually occur in the late stages of AIDS, sometimes as incidental findings with minor symptoms. Treatment is difficult and often unsuccessful.

M. tuberculosis is seen more commonly in patients with AIDS than in the general population and occurs earlier in the disease than the atypical mycobacteria. The patients usually present with fever, cough, and sputum production. Treatment is with conventional therapy, pyrazinamide, ethambutol, rifampicin, and isoniazid for two months, followed by Rifinah (rifampicin plus isoniazid) for a further four months.

Bacterial pneumonia—Pneumonia caused by conventional bacterial pathogens is more common in patients with AIDS (17.0/1000) than in the general population (2.6/1000). *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common pathogens. Fever, cough, and occasionally pleuritic pain are the presenting features, which are often identical with those seen in patients without AIDS. Treatment is with an appropriate antibiotic.

Fungi—Fungi are rarely seen, accounting for less than 1.6% of cases in the United States of America and even less in the United Kingdom. Treatment is with amphotericin B at 0.6 mg/kg/day.

Kaposi's sarcoma—Necropsy studies show that most patients with Kaposi's sarcoma have some pulmonary disease, but few have had symptoms from this. Those who do have symptoms usually present with increasing breathlessness, cough, and occasional haemoptysis. Treatment with chemotherapy has been largely unsuccessful and in widespread lung disease radiotherapy is inadvisable.

Lymphoid interstitial pneumonia and alveolar proteinosis—Both these conditions have been described in patients with AIDS. Lymphoid interstitial pneumonia is considered to be a primary disease, though it may be a response to a hitherto unknown viral agent. Alveolar proteinosis has been seen in association with opportunistic infection.

Investigation and diagnosis

Cytology preparation of induced sputum showing macrophage containing many cysts of *Pneumocystis carinii* (Grocott's methenamine silver stain). (Courtesy of Dr Gabriella Kocjan.)

Transbronchial biopsy specimen in patient with pneumocystis pneumonia showing alveoli filled with material which appears pink and "foamy" with periodic Schiff staining (x 200). (Courtesy of Dr Meryl Griffiths.)

Transbronchial biopsy in patient with pneumocystis pneumonia showing cysts of *Pneumocystis carinii* stained with Grocott's methenamine silver (x 1000). (Courtesy of Dr Meryl Griffiths.)

Invasive and non-invasive methods of investigation are described below in the sequence in which they are routinely performed after clinical examination.

Chest radiograph

In *Pneumocystis carinii* pneumonia the initial radiographic feature is a perihilar haze which progresses to diffuse symmetrical shadowing of the mid and lower zones with peripheral sparing. There are no diagnostic radiographic features. However, in a recent United Kingdom series there were atypical x ray features in all but two cases, in which *Pneumocystis carinii* pneumonia was not the diagnosis. In early cases the radiograph may be entirely normal. Cytomegalovirus pneumonitis may produce similar changes. Kaposi's sarcoma can produce widespread changes but usually of a more nodular appearance than in *Pneumocystis carinii* pneumonia. Pleural effusions are most commonly due to Kaposi's sarcoma. In bacterial infections radiographic changes are usually localised, producing areas of focal consolidation.

Blood gases

Arterial blood gas tensions are usually abnormal, with hypoxia and hypocarbia. Measurement of gas tensions is essential for early detection of hypoxia and its treatment with oxygen.

Induced sputum

Many patients, particularly those with *Pneumocystis carinii* pneumonia, have a non-productive cough. The use of 3% saline through a nebuliser at a flow rate of 8 litres per minute for 5 to 20 minutes has been helpful in inducing sputum production. Examining the sputum has been reported to detect up to half of cases of *Pneumocystis carinii* pneumonia subsequently diagnosed at bronchoscopy. Trophozoites and precyst forms (detected by GIEMSA staining) predominate over cystic forms (detected by methenamine silver staining) in sputum. Sputum can also be cultured for bacteria, mycobacteria, and fungi.

Bronchoscopy

Bronchoalveolar lavage and transbronchial biopsy give high diagnostic yields—88% and 85% respectively and greater than 90% in combination. In a patient with focal radiographic changes in whom induced sputum gives no diagnosis it is the immediate investigation. Endobronchial abnormalities such as Kaposi's sarcoma may be seen, though this does not correlate well with parenchymal disease. Lavage is performed ideally under fluoroscopic control, particularly if radiographic changes are focal.

Bronchoscopy is uncomfortable, requires a trained physician, and complications of bleeding and pneumothorax, though rare, may occur. Arterial oxygen concentrations and a clotting screen must be obtained before this procedure. Bronchoscopy is usually performed to obtain a definite diagnosis. But in the future this may not be possible or even desirable as the workload increases and scientific evidence accumulates to determine the accuracy of clinical diagnosis in most instances.

The bronchoscopist should wear a mask, goggles and gloves, and ideally waterproof overclothing. The bronchoscope should be thoroughly cleaned in a conventional manner and then soaked in glutaraldehyde for one hour. It can then be used for any patient without any fear of infection being transmitted. A non-immersible bronchoscope has to be gas sterilised with ethylene oxide. The biological control used for this process means that five days must elapse before sterility can be ensured.

Lung function tests

Transfer factor in patients is usually lowered in *Pneumocystis carinii* pneumonia; in one reported series only seven out of 91 patients with *Pneumocystis carinii* pneumonia had normal values. Spirometry and lung gas volumes are non-specific, though often abnormal. We do not perform tests of lung function routinely.

Bronchoalveolar lavage

- Cytology
- Microbiology
- Virology (cytomegalovirus, cytopathic effect in cell culture. In some centres detection of α and β proteins (early proteins produced in cytomegalovirus replication 4-6 hours after cell infection)

Transbronchial biopsy

- Histology
- Microbiology (fungi, alcohol and acid fast bacilli, bacteria)
- Virology

Gallium scanning has been used extensively in the United States in patients with AIDS but less so in the United Kingdom. Gallium scans are frequently abnormal in *Pneumocystis carinii* pneumonia but also in the other respiratory manifestations of AIDS and are non-specific. We do not use this technique in our patients.

Open lung biopsy

This procedure may often be the only method to diagnose parenchymal Kaposi's sarcoma or lymphoid interstitial pneumonia.

Mechanical ventilation

Whatever the diagnosis or method used to achieve it, some patients will progress to respiratory failure, often rapidly, and the question of ventilation will arise. Experience with mechanical ventilation has shown universally poor results. In one large series no patient who had survived ventilation was alive at one year. Patients with *Pneumocystis carinii* pneumonia who do not respond to therapy and go into respiratory failure rarely improve through mechanical ventilation. There cannot be a uniform policy but mechanical ventilation seems appropriate as an exception rather than the rule.

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Lesson of the Week

Complacency in diagnosis of cervical cancer

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Death from cervical cancer should be preventable. The pre-malignant stages of cervical neoplasia are well defined¹ and may be detected by a simple screening test² and treated by conservative measures with high rates of primary cure.³ When invasive cancer occurs it is often associated early in its course with characteristic symptoms: vaginal discharge, postcoital bleeding, intermenstrual bleeding, and postmenopausal bleeding in older women. Many cases should therefore be diagnosed before the disease has spread, allowing radical treatment and a favourable outcome.

Despite at least a fourfold increase in the number of cervical smears taken in England and Wales over the past 20 years there has been only a small decrease in deaths from cervical cancer.⁴ During this period there has been a dramatic increase in deaths from the disease among young women aged under 35,⁵ with the attendant threat of future increases in deaths from cervical cancer at older ages.⁶ This failure to reduce mortality from cervical cancer, particularly in younger women, is an indictment not only of

All women in whom a cervical smear shows dyskaryotic cells should be referred for colposcopy. This applies equally to young women, in whom mortality from cervical cancer has increased appreciably

government screening policies but also of doctors' failure to recognise fundamental aspects of the course of preinvasive cervical neoplasia and the clinical presentation of cervical malignancy.

The failure of the screening programme for cervical cancer in England and Wales to produce the considerable decrease in mortality from cervical cancer that has occurred elsewhere, particularly in Scandinavia,⁷ has been the subject of much controversy. Much attention has focused on the administrative failures in the cervical cytology screening programme: some workers have claimed that all the scientific facts needed to save most of the lost lives have been known for 20 years and the blocks to effective action are neither scientific nor technical but administrative.⁸

Although some administrative features of the screening programme for cervical cancer require review, failure to respond appropriately to abnormal cervical smears and a seemingly complacent attitude to symptoms and signs of cervical cancer are important factors. This is highlighted by the case histories of 14

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