

# Respiratory manifestations

# 14

## 14.1 Approach to respiratory symptoms

**Ian Woolley**

Department of Infectious Diseases, Monash Medical Centre and Department of Medicine, Monash University, Melbourne, VIC

**Jeffrey J Post**

Department of Infectious Diseases and Albion Street Centre, Prince of Wales Hospital and School of Medical Sciences and Prince of Wales Clinical School, University of New South Wales, Sydney, NSW

The approach to respiratory disease in patients with HIV involves a synthesis of symptoms, signs, risk-factor history, knowledge of the patient's degree of immunodeficiency, chest radiography and sputum sampling. More specialised investigations such as lung-function testing, computed tomography (CT) of the chest, radionuclide studies, bronchoscopy or lung biopsy may be required to make a diagnosis. Multiple disease processes may affect the respiratory system in HIV infection (Table 14.1) and multiple pathological processes can occur simultaneously, especially in advanced immunodeficiency. Non-infective respiratory disorders may also occur.

Opportunistic respiratory disease no longer predominates as the cause of respiratory symptoms in the era of combination antiretroviral therapy (cART). It is important therefore to consider the differential diagnosis of symptoms according to level of immunodeficiency and treatment with cART. The onset of respiratory symptoms within a few months of initiating cART in an immunocompromised patient suggests the possibility of immune reconstitution disease.<sup>1</sup>

### 14.1.1 Immunodeficiency

Knowledge of the level of immunodeficiency, as in many aspects of HIV disease, provides a guide to the likely differential diagnoses. People with significant immunodeficiency (e.g. CD4 cell count <200 cells/ $\mu$ L or <14% of total lymphocyte count) are at increased risk of opportunistic infections, including *Pneumocystis jirovecii* pneumonia (PJP) (previously *Pneumocystis*

*carinii* pneumonia [PCP]). Bacterial pneumonia can occur at any CD4 cell level, but occurs more frequently in immunodeficient people than in those with a preserved CD4 cell count, often in association with bacteraemia. Non-Hodgkin's lymphoma and tuberculosis (TB) can occur at any level of immunodeficiency, although TB is more likely to involve extrapulmonary sites in immunodeficient patients. More severe immunodeficiency (CD4 cell count <100 cells/ $\mu$ L) is associated with an increased risk of *Toxoplasma gondii* pneumonitis and cryptococcal pulmonary pathology. At this level of immunodeficiency, staphylococcal and gram-negative bacterial pneumonia occur more frequently than in people with CD4 cell counts >100 cells/ $\mu$ L. Infections with *Streptococcus pneumoniae* and *Haemophilus* spp. also occur. In the profoundly immunodeficient person (CD4 cell count <50 cells/ $\mu$ L), both cytomegalovirus (CMV) and *Mycobacterium avium* complex may be associated with pneumonitis, usually in the context of disseminated disease. It is important to remember that all opportunistic infections may rarely occur at higher CD4 cell counts, especially in the setting of antiretroviral therapy.

### 14.1.2 Clinical history Symptoms

Certain features in the patient's history may be suggestive of one disease process over another. Typically, PJP is a subacute illness of fatigue, fever and dry cough of several weeks' duration. In comparison, symptoms of short duration (hours to days), including chest pain, abrupt onset of fever and rigors

**Table 14.1** Differential diagnosis of causes of respiratory illness

Bacterial	Fungal	Viral	Parasitic	Malignant	Others
<i>Streptococcus pneumoniae</i>	<i>Pneumocystis jirovecii</i>	Cytomegalovirus	<i>Toxoplasma gondii</i>	Kaposi's sarcoma	Chronic airflow limitation/emphysema
<i>Haemophilus influenzae</i>	<i>Cryptococcus neoformans</i>	Influenza		Non-Hodgkin's lymphoma	Pneumothorax (in <i>Pneumocystis jirovecii</i> pneumonia)
<i>Mycobacterium tuberculosis</i>	<i>Aspergillus</i> spp.			Carcinoma of the lung	Pulmonary hypertension
<i>Moraxella catarrhalis</i>	<i>Candida</i> spp.				Cardiac failure
<i>Pseudomonas aeruginosa</i>	Dimorphic fungi ( <i>Coccidioides immitis</i> and <i>Histoplasma capsulatum</i> )				Pericardial effusion
Gram negative enterobacteriaceae	<i>Penicillium marneffeii</i>				Lymphocytic interstitial pneumonia
<i>Rhodococcus equi</i>					Bronchitis
<i>Staphylococcus aureus</i>					Sinusitis
<i>Nocardia</i> spp.					Pulmonary emboli
<i>Legionella</i> spp.					

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and a productive cough are more consistent with bacterial (e.g. pneumococcal) pneumonia. Dyspnoea may occur in a range of infective pathological processes, but may also be the only symptom of cardiomyopathy, ischaemic heart disease or pulmonary hypertension.

### Prophylactic therapies

Immunodeficient patients who are taking PJP prophylaxis are nine times less likely to develop PJP than those not taking PJP prophylaxis.<sup>2</sup> Prophylactic treatment with cotrimoxazole (sulphamethoxazole/trimethoprim) is likely to reduce the incidence of bacterial infections as well as PJP and *Toxoplasma gondii* reactivation. Persons with a positive Mantoux test (>5 mm) who have not received treatment for latent TB have a 14% risk of developing active tuberculosis over a two-year period and should therefore be considered for isoniazid prophylaxis.<sup>3</sup> The data on gamma interferon release assays, such as Quantiferon Gold or ELISPOT testing, in the setting of HIV are limited. It is uncertain if there is a clinical benefit of isoniazid treatment for latent TB infection when defined by a positive gamma interferon release assay if the Mantoux test is less than 5 mm (see Section 13.5).

### Travel history

Persons who have resided in or travelled to countries with a high prevalence of TB are at increased risk for disease. Travel to areas endemic for the dimorphic fungi may be important: *Histoplasma capsulatum* is endemic in areas of the USA (especially the Mississippi and Ohio River valleys), Latin America, West Indies, Eastern India, and Africa. *Coccidioides immitis* is hyperendemic in some parts of the southwest of the USA, Northern Mexico, and in Central and South America. Other illnesses with respiratory symptoms where a travel history might be important include melioidosis, penicilliosis, strongyloidiasis and *Salmonella* infection.

### Other aspects

Smoking is an important risk factor for bacterial pneumonia, bronchitis, chronic airflow limitation and carcinoma of the lung in the population with HIV, as in the general population. Marijuana smoking has been associated with *Aspergillus*

infection.<sup>4</sup> A contact or occupational history may also be useful in suggesting the possibility of TB. A past history of incomplete treatment of TB may suggest drug-resistant disease. Current injecting drug use is a risk factor for infective endocarditis and staphylococcal pneumonia. Men who have sex with men are more likely to develop Kaposi's sarcoma (KS), although isolated pulmonary disease without mucocutaneous lesions is uncommon.<sup>5</sup> Antiretroviral treatment itself may be a cause of respiratory symptoms, e.g. dyspnoea caused by nucleoside analogue-induced lactic acidosis, hypersensitivity reaction to abacavir (now largely eliminated by HLAB57\*01 testing) and the largely unexplained increased incidence of bacterial pneumonias associated with enfuvirtide use.

### 14.1.3 Physical examination

The physical examination may be normal in patients with HIV with PJP, aside from tachypnoea and a dry cough, although fine crackles may be present. Signs of consolidation suggest bacterial, mycobacterial or fungal disease. Examination for extrapulmonary features should be undertaken, as disseminated disease processes may present with pulmonary symptoms. Cardiovascular signs should be assessed as pulmonary hypertension, endocarditis, cardiomyopathy and pericardial effusions may also cause breathlessness. Signs associated with immunodeficiency should be elicited (e.g. oral candidiasis) as these may influence the differential diagnosis in the absence of a current CD4 cell count. The skin should be examined for the presence of KS and the cutaneous lesions of cryptococcosis. The presence of neurological signs may suggest disseminated toxoplasmosis, and drowsiness may occur in cryptococcosis. Hepatosplenomegaly may be present in persons with *Mycobacterium avium* complex infection, non-Hodgkin's lymphoma or CMV infection.

### 14.1.4 Investigations

#### Blood tests

Most standard biochemical and haematological tests are not helpful in the diagnosis of respiratory symptoms in advanced HIV disease. However, peripheral blood neutrophilia and left shift may occur in bacterial pneumonia and cryptococcal disease. Neutropenia may suggest an increased likelihood of

Table 14.2 Differential diagnosis of chest radiograph abnormalities

	PJP	Bacteria	M. TB	Fungi	NHL	KS	MAC	CMV
Normal	Yes		Yes	Yes		Yes		
Focal consolidation/ infiltrate	Yes	Yes	Yes	Yes	Yes			
Miliary	Uncommon		Yes	Yes				
Diffuse or multifocal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reticular or granular	Yes	Yes	Yes	Yes	Yes			Yes
Nodular	Uncommon	Yes	Yes	Yes	Yes	Yes		
Cystic lesions	Yes			Yes				
Cavities	Uncommon	Yes	Yes	Yes				
Pneumothorax	Yes	Uncommon	Uncommon					
Lymphadenopathy			Yes	Yes	Yes	Yes	Yes	
Pleural effusions		Yes	Yes	Yes	Yes	Yes		

CMV = cytomegalovirus; KS = Kaposi's sarcoma; MAC = *Mycobacterium avium* complex; M.TB = *Mycobacterium tuberculosis*; NHL = non-Hodgkin's lymphoma; PJP = *Pneumocystis jirovecii* pneumonia.

Adapted from Table 13.5 in Morris A, Huang L. Evaluation and management of respiratory complications of HIV infection. In: Crowe S, Hoy J, Mills J, editors. Management of the HIV-infected patient. London: Martin Dunitz; 2002:217.

**Table 14.3 Recommended investigations in respiratory illness**

Regular investigations
Full blood count and differential
CD4 cell count
Expectorated sputum examination – bacteriology, <i>Pneumocystis jirovecii</i> immunofluorescence, acid fast stain, fungal culture
Induced sputum – if CD4 cell count <200cells/μL <i>P. jirovecii</i> immuno-fluorescence
Chest radiograph
Arterial blood gases
Blood cultures – bacterial, mycobacterial if CD4 cell count <50 cells/μL
Supplemental investigations
Computed tomography of chest – high resolution
Bronchoscopy with bronchoalveolar lavage
Electrocardiograph
Echocardiography – pericardial effusion, cardiomyopathy, pulmonary hypertension
Ventilation perfusion lung scan
Pulmonary diffusing capacity/spirometry
Serum cryptococcal antigen titre
Examination of other organs if involved (e.g. bone marrow biopsy if pancytopenic)
Lung biopsy

bacterial or fungal infection. Measurement of the degree of impairment of gas exchange with arterial blood gas analysis is important, as the degree of hypoxaemia may change the management of certain diseases (e.g. steroid therapy in PJP). In cases of suspected cryptococcal disease, the titre of serum cryptococcal antigen is used as evidence of disseminated disease. Bacterial blood cultures should be obtained as well as mycobacterial blood cultures in immunodeficient patients, given the elevated rates of bacteraemia.

### Chest radiograph

The chest radiograph may reveal the presence of focal consolidations suggestive of bacterial, tuberculous, cryptococcal or lymphomatous disease. The typical radiological pattern of TB, with upper lobe disease and cavitation, may not be seen in immunodeficient people. Pleural effusions may be caused by KS or the range of diseases which also cause consolidation. The presence of a pleural effusion makes the likelihood of PJP quite low, although in advanced HIV disease, multiple disease processes may co-exist. The presence of a pneumothorax makes PJP more likely, although other disease processes may rarely cause a bronchopleural fistula and be associated with a pneumothorax. Cavitating disease is likely to be caused by *Mycobacterium tuberculosis*, bacteria, fungi, *Nocardia* spp., and some atypical mycobacteria. Diffuse infiltrates with a reticular or granular pattern are consistent with PJP, but many other diseases may have a similar radiographic pattern. A normal chest radiograph does not exclude PJP. Similarly, a normal radiograph may be seen in cases of TB or cryptococcosis where extrapulmonary disease is the major manifestation.<sup>6</sup> (Table 14.2 and 14.3.)

### Other investigations

Sputum from all patients with HIV presenting with productive cough should be sent for microscopy and culture. Sputum investigations should routinely include Gram stain, bacterial and fungal culture and sensitivity testing. Although not all specimens need to be examined for mycobacteria, a low threshold for testing sputa for acid-fast bacilli and mycobacterial culture should be maintained. An induced sputum should be collected where the clinical likelihood of PJP is high, provided adequate negative-pressure facilities exist. The sample is assessed for the presence of *P. jirovecii* by immunofluorescence, Giemsa or silver stains and a result is usually available within two hours. More recently PCR testing for *Pneumocystis* has been developed, but the use of this technology is limited by poor specificity for disease.<sup>7</sup> Induced sputum which is negative for *P. jirovecii* does not exclude the diagnosis of PJP. Supplemental investigations such as bronchoscopy increase the diagnostic yield for *P. jirovecii*, and may facilitate other diagnoses as well. *P. jirovecii* may still be detected by bronchoscopy and bronchoalveolar lavage after several days of therapy with cotrimoxazole. A high resolution CT scan that does not reveal 'ground glass' changes makes the diagnosis of PJP unlikely.<sup>8</sup> Similarly, the pulmonary diffusing capacity is typically reduced and lung clearance of technetium is typically increased in PJP. The absence of these findings suggests that alternative pathology to PJP should be considered. Where a pleural effusion has been detected, a diagnostic pleurocentesis is warranted. Pulmonary nodules should be biopsied if sputum sampling, bronchoscopy and less invasive investigations are negative (e.g. serum cryptococcal antigen or bone marrow biopsy in the setting of pancytopenia).

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## 14.2 Respiratory infections

Ian Woolley

Department of Infectious Diseases, Monash Medical Centre and Department of Medicine, Monash University, Melbourne, VIC

Cassy Workman

Ground Zero Medical Centre, Sydney, NSW

### 14.2.1 Bacterial pneumonia

Bacterial pneumonia is a significant cause of morbidity and mortality in people with HIV. This infection is predominantly caused by *Streptococcus pneumoniae*. People with HIV are at much higher risk of invasive pneumococcal infection than the general population, with the incidence of pneumococcal bacteraemia 100 times that of age-matched populations, and pneumococcal pneumonia rates five to 17 times those of the general population.<sup>1</sup> Children with HIV infection appear to be at even greater risk of invasive pneumococcal disease. Recurrent pneumococcal infection is more common in patients with HIV than the general population.<sup>1</sup>

Risk factors for pneumococcal infection in patients with HIV infection include cigarette smoking (both active and passive forms), injecting drug use, recent hospital admission, blood transfusion as the mode of HIV transmission, alcoholism, a previous AIDS-defining illness and previous pneumococcal infection.<sup>1-4</sup> The risk of pneumococcal infection is greater in individuals with CD4 cell counts <500 cells/ $\mu$ L compared with >500 cells/ $\mu$ L, and is greatest with CD4 cell counts <200 cells/ $\mu$ L.<sup>1</sup> Infection with *S. pneumoniae* which has reduced sensitivity to penicillin occurs at a similar frequency in people with HIV infection and the general population.<sup>5</sup>

#### Clinical presentation

People with HIV with *S. pneumoniae* infection most commonly present with pneumonia. The major symptoms are fever (96%), cough (90%) and dyspnoea (72%).<sup>1</sup> Bacterial pneumonia due to *Haemophilus influenzae* may be indistinguishable from *S. pneumoniae*. In advanced immunosuppression, pneumonia secondary to *Pseudomonas aeruginosa* and to *Staphylococcus aureus* increases in frequency and may present with cavitary infiltrates. Rare presentations of pneumococcal infection include mediastinitis, multiple brain abscesses, meningitis,<sup>6</sup> pericarditis and endocarditis,<sup>7</sup> cervical cellulitis,<sup>8</sup> and testicular abscess.<sup>9</sup>

#### Diagnosis

The diagnosis is usually clinical. Nevertheless, blood should be sent for culture. Blood cultures are the most sensitive diagnostic tool, with isolation of *S. pneumoniae* in 85% of patients.<sup>1</sup> Leukocytosis may not occur, but a left shift with band forms may be observed. Chest x-ray findings include segmental, lobar or multilobar consolidation, although interstitial infiltrates are found in some patients.<sup>1</sup> Thoracentesis should be considered for patients with pleural effusions if there is clinical concern of empyema.

#### Management

Decisions on treatment are based on the severity of the pneumonia. Treatment for bacterial pneumonia is the same for those with HIV and the general population. For cases of mild-to-moderate pneumonia, amoxicillin 1 g three times daily may be used with or without a macrolide or doxycycline if atypical pneumonia is suspected. However, if parenteral

therapy is required, intravenous benzyl penicillin (penicillinG) 1.2 g every six hours is recommended. In patients with penicillin allergy, roxithromycin 300 mg daily may be used, or for parenteral therapy, cefalothin 1g every six hours. In severe pneumonia, intravenous ceftriaxone 1 g daily (or benzyl penicillin 1.2 g every four hours with gentamicin) plus azithromycin 500 mg daily or erythromycin 1 g six hourly are recommended. Specific recommendations exist for tropical areas of northern Australia.<sup>10</sup>

#### Prevention

The role of 23-valent pneumococcal polysaccharide vaccine has been controversial. Its use has been recommended by authorities in the USA, Europe, Brazil and Australia.<sup>11,12</sup> A randomised, placebo-controlled study in African adults showed no decrease in pneumococcal disease in the vaccinated group compared with the placebo group.<sup>13</sup> Importantly, this study also showed an increased risk for all types of pneumonia in the vaccine arm. However, other studies have shown an overall benefit from vaccination,<sup>14</sup> and both combination antiretroviral therapy (cART) and vaccination with pneumococcal vaccine had independent protective effects against pneumococcal infection regardless of CD4 cell count. Most authorities would now therefore favour vaccination in resource replete settings.<sup>15</sup>

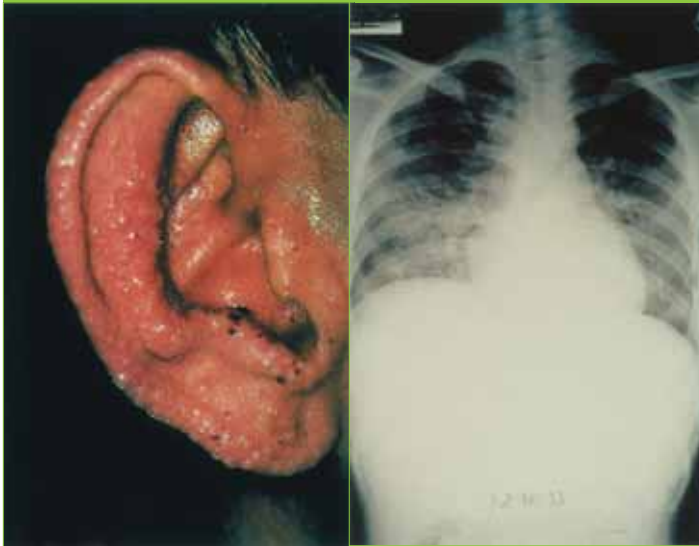
### 14.2.2 Penicilliosis

Penicilliosis is a systemic mycotic infection, caused by *Penicillium marneffe*, a dimorphic fungus endemic in South-East Asia, Hong Kong and parts of southern China. *P. marneffe* was first isolated from a species of bamboo rat; however, the environmental source of infection remains unclear.<sup>16</sup> Infection is thought to occur by the respiratory route. An increased risk is seen with recent occupational exposure to soil.<sup>16</sup> Symptomatic infection occurs only rarely in the immunocompetent host. Clinical presentation may occur many years after exposure.<sup>17</sup> The rapid explosion of HIV in the areas endemic for this fungus has led to a significant increase in cases of *P. marneffe* infection with more than 1000 cases reported in a seven-year period at one hospital in Thailand alone.<sup>18</sup> Increased incidence occurs during the wet season (May to October).

#### Clinical presentations

*P. marneffe* infection is usually reported in late stage HIV disease when the CD4 cell count is <100 cells/ $\mu$ L.<sup>16,18</sup> The presentation is subacute with constitutional signs and symptoms. Fever and weight loss occur in 95% of patients. Cough and pulmonary symptoms occur in up to one-third of patients. On examination, lymphadenopathy and hepatomegaly are seen in 70% of patients, and concomitant oral candidiasis in 50%. Characteristic skin lesions, cutaneous papules with central necrotic umbilication resembling molluscum contagiosum are present in 70% of patients (Image 14.1). These lesions are similar to those seen in histoplasmosis and cryptococcosis, but are distributed predominantly on the upper parts of the body (scalp, face, upper extremities and trunk).<sup>16</sup> Disseminated disease

Image 14.1 Penicilliosis



Source: Stewart G. Managing HIV with limited medical resources. In: Stewart G, editor. Managing HIV. Sydney: Australasian Medical Publishing Company Ltd.;1997:194. Used with permission.

is common at presentation, with possible lung, liver, spleen and bone involvement. In contradistinction to both histoplasmosis and cryptococcosis, dissemination to the central nervous system does not occur with *P. marneffei*.<sup>16</sup> The reason for this lack of neurotropism is not clear. Anaemia and abnormal liver function tests are also frequently present. In patients with lung involvement, x-ray findings include nodules, interstitial infiltrates and pleural effusion. There has been a series of patients with hepatic disease who lacked skin manifestations, but whether this indicates a different form of the disease is not clear.<sup>19</sup> Immune reconstitution features have not been described.

## Diagnosis

Diagnosis is confirmed by fungal culture or histopathology of a specimen obtained from a normally sterile site (i.e. blood, skin lesions, bone marrow, lymph node, liver). Isolation occurs most frequently from bone-marrow aspirates and lymph-node samples (100%), followed by skin biopsy (90%) and blood cultures (76%).<sup>16</sup> Full identification of the organism may take up to seven days. Galactomannan (GM) is a heteropolysaccharide in the cell walls of most *Aspergillus* and *Penicillium* species. The use of the GM antigen assay may facilitate earlier diagnosis of *P. marneffei* infection for patients with HIV in areas of endemicity, as 73% of patients have positive tests, particularly those with fungaemia.<sup>20</sup> Research continues on a serological assay and polymerase chain reaction assay to assist in diagnosis, but these tests are not currently available for clinical use.

## Management

Therapy for penicilliosis depends on severity of disease. Mild-to-moderate disease can be treated with itraconazole 200 mg per day. Severe disease requires treatment with amphotericin B (0.5-1.0 mg per kg per day) for induction therapy followed by itraconazole (400 mg per day) as maintenance therapy. Measurement of itraconazole levels is recommended. Relapse rates without maintenance therapy approach 50%.<sup>21</sup> Maintenance therapy with itraconazole (200 mg daily) should be continued lifelong.<sup>18</sup> Relapse occurs infrequently in the presence of maintenance therapy, although it is more likely in

patients who remain in endemic areas.<sup>16</sup> There have been recent reports of successful discontinuation of maintenance therapy in patients who have achieved immune reconstitution with antiretroviral therapy (CD4 cell count >100 cells/ $\mu$ L for six months).<sup>22,23</sup>

In patients with HIV infection and a CD4 cell count <200 cells/ $\mu$ L who live in an endemic area, primary prophylaxis with itraconazole at a dose of 200 mg per day is recommended.<sup>24</sup>

## 14.2.3 Nocardiosis

Originally considered a fungus, *Nocardia* species are a group of ubiquitous actinomycetes. Nocardial taxonomy is complex and, of the nine species described, only seven have been associated with human disease, with *N. asteroides* the most commonly identified.<sup>25</sup> Although distributed worldwide, disease is most common in men. A preponderance of cases occur in rural areas, probably reflecting exposure via contact with soil.<sup>26</sup> *Nocardia* spp. may cause cutaneous, pulmonary or disseminated disease. Dissemination is thought to occur primarily from the lung, but in the case of injecting drug users with HIV the occurrence of

mediastinal disease exclusive to this population suggests direct intravenous contamination as the portal of entry.<sup>27</sup> Pulmonary and disseminated disease occur almost exclusively in association with defects in cell-mediated immunity, immunoglobulin production or leukocyte function.<sup>28</sup> Prevalence in people with HIV infection is low, varying from 0.3-1.8%,<sup>29,30</sup> although one West African autopsy study showed 4% of patients with pulmonary nocardial infection.<sup>31</sup> Infection in people with HIV is strongly associated with injecting drug use<sup>27,30</sup> and advanced immunosuppression with a CD4 cell count of <200 cells/ $\mu$ L.<sup>32</sup>

## Clinical presentation

Cutaneous disease may present as one of four types: mycetoma; lymphocutaneous (sporotrichoid) infection; acute cutaneous infection; or systemic disease with cutaneous involvement. Multiple types may occur in the same person. Mycetoma is a chronic, indurated, granulomatous, subcutaneous infection consisting of nodules and draining sinus tracts, often localised to the site of inoculation.<sup>33</sup> The discharge from these sinus tracts often contains small white granules consisting of masses of mycelia. Dissemination from mycetoma is rare, but local invasion from head and neck lesions may result in severe disability or death. Lymphocutaneous disease also develops as a nodule at the site of inoculation; however, central ulceration rather than draining sinus formation occurs, and as ulceration spreads to the lymph nodes, multiple subcutaneous nodules develop along the draining lymphatics.<sup>34</sup> (Image 14.2) Acute cutaneous infection may manifest as a superficial skin infection with pustules, abscesses, cellulitis, granulomas and ulcers,<sup>34</sup> (Image 14.2).

Pulmonary disease is the most common manifestation of nocardial infection in the immunocompromised patient, typically presenting as a subacute illness. Fever and cough with thick purulent sputum are usually present; other constitutional signs are variable.<sup>35</sup> Chest x-ray findings are variable and may consist of a necrotising pneumonia with cavitation formation, infiltrates of varying size, single or multiple nodules which are highly suggestive of malignant tumours,<sup>36</sup> and pneumonia-associated empyema.<sup>37</sup> Pulmonary infections have a propensity

Image 14.2 Localised nocardial infection



Source: Allworth AL, Bowden FJ. HIV and bacterial infections. In: Stewart G, editor. Managing HIV. Sydney: Australasian Medical Publishing Company Ltd; 1997:112.

for haematogenous spread with extrapulmonary dissemination occurring in half of all patients and seeding of the central nervous system (CNS) occurring in one third.<sup>35</sup> Brain abscesses, usually supratentorial, are the most common CNS presentation; meningitis is rarely reported.<sup>37</sup> Clinically silent CNS involvement is sufficiently common that cerebral-imaging studies are recommended, preferably magnetic resonance imaging (MRI), in all patients.<sup>38</sup> Immune reconstitution features have not been reported in nocardial infection.

## Diagnosis

A high index of suspicion for *Nocardia* may be the most useful aid in diagnosis. In all suspected cases, early notification to the microbiology laboratory is essential. Sputum or pus should be examined for weakly acid-fast, gram-positive filamentous bacteria. Sputum smears are often negative, and bronchoscopy or lung aspiration is usually necessary. *Nocardia* grow quite slowly, and colonies may take up to four weeks to develop.<sup>39</sup> 30% of patients with *Nocardia* detected in blood cultures also have concomitant bacteraemia with other pathogens.<sup>37</sup> If cerebrospinal fluid or urine is used for culture, specimens should first be concentrated to optimise yield.

## Management

The treatment of nocardial infections may include both surgical and medical interventions; however, prospective, controlled, clinical trial data are lacking. Antibiotics should not be delayed as early administration has been shown to improve outcomes.<sup>40</sup> Sulphonamides are the best studied drugs,<sup>41</sup> with trimethoprim-sulfamethoxazole (cotrimoxazole) the most frequently used formulation, despite limited efficacy data and poor *in vitro* results. Minocycline generally has excellent *in vitro* activity, and has been successfully used at doses of 100-200 mg twice daily as an alternative agent in pulmonary and even cerebral infection.<sup>26</sup> Other useful drugs in the management of nocardial infection include imipenem, meropenem, cefotaxime, ceftriaxone, amikacin, and amoxicillin/clavulanic acid.<sup>39,42,43</sup> Therapy should be continued in the immunosuppressed person for at least 12 months, as shorter durations of therapy have been associated with relapse and increased mortality.<sup>40,44</sup> In cases of disseminated infection, therapy should include at least two active agents. In CNS infections, cotrimoxazole is generally used in combination with imipenem, meropenem, amikacin or a third-generation

cephalosporin. Different *Nocardia* species may differ in their *in vitro* susceptibility to antibiotics, and species identification is critical to guiding the selection of therapeutic agents.<sup>26</sup>

## Prophylaxis

Although it is often stated that cotrimoxazole reduces the risk of nocardiosis in persons with HIV disease, there is no compelling clinical evidence to support this claim, especially at the doses used for PJP prophylaxis.<sup>27,29,30</sup> Indeed, there are numerous case reports of patients who develop nocardiosis despite receiving cotrimoxazole prophylaxis.

## Prognosis

The mortality rate in pulmonary disease and extrapulmonary dissemination is high, with rates of 60% to 85% reported.<sup>30,39</sup>

### 14.2.4 *Rhodococcus equi*

*Rhodococcus equi* (formerly called *Corynebacterium equi*) is an aerobic, gram-positive, weakly acid-fast, non-spore forming coccobacillus. *R. equi* was first isolated from horses and has been widely reported as a pathogen in domestic animals. However, contact with either farm environments or animals is rarely documented in people with HIV with *R. equi* infection.<sup>45-47</sup> *R. equi* is usually acquired through the respiratory route in both animals and humans although person-to-person and nosocomial transmissions have been described.<sup>45,48</sup>

## Clinical presentation

*R. equi* infection in people with HIV presents with pulmonary involvement, usually accompanied by bacteraemia and frequent dissemination to extrapulmonary sites.<sup>48,49</sup> *R. equi* infection usually presents subacutely with fever and cough. Weight loss, pleuritic chest pain and hemoptysis are also frequently reported.<sup>45,50-52</sup> *R. equi* infection in people with HIV usually occurs at CD4 cell counts <200 cells/ $\mu$ L, and concomitant infections with other opportunistic infections occur frequently.<sup>45,47,51</sup> Radiological features consist of cavitating lesions with a strong predilection to involvement of the upper lobe (50-75% of cases). Consolidation is also frequently seen. However, in one case series normal chest x-ray findings were reported in one-quarter of patients.<sup>45</sup> Both the clinical picture and x-ray findings may suggest infection with *Mycobacterium tuberculosis* or *Nocardia* spp.<sup>47,52</sup> Histological examination demonstrates multiple microabscesses with dense infiltration by histiocytes and intracellular gram-positive coccobacilli.<sup>49</sup> Immune reconstitution features have not been described.

## Diagnosis

*R. equi* can be cultured from blood, sputum, bronchoalveolar washings and biopsy material using standard media.<sup>53</sup> *R. equi* resembles oropharyngeal commensal diphtheroids and is frequently regarded as a contaminant, leading to late diagnosis in many cases.<sup>50-52</sup>

## Management

The optimal choice and duration of antibiotic therapy for *R. equi* infection remains to be determined.<sup>50,54</sup> Based on *in vitro* susceptibility, *R. equi* is sensitive to erythromycin, rifampicin, vancomycin, gentamicin and ciprofloxacin. Initial therapy with erythromycin or imipenem plus rifampicin for at least two weeks is recommended. Ciprofloxacin is an alternative agent, but ciprofloxacin-resistant strains from South-East Asia have been reported. Surgical intervention is sometimes needed and lifelong, suppressive, oral therapy with a macrolide and rifampicin is recommended.<sup>46,51</sup> Mortality in patients with HIV with *R. equi* is high, often with death the result of other concomitant infections.<sup>45</sup>

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## 14.3 Respiratory disorders

Ian Woolley

Department of Infectious Diseases, Monash Medical Centre and Department of Medicine, Monash University, Melbourne, VIC

Jeffrey J Post

Department of Infectious Diseases and Albion Street Centre, Prince of Wales Hospital and School of Medical Sciences and Prince of Wales Clinical School, University of New South Wales, Sydney, NSW

### 14.3.1 Sinusitis

Sinusitis is a common problem in people with HIV; in one retrospective review of hospitalised patients, 11% of patients were affected by this disorder.<sup>1</sup> Sinusitis is more common with immunodeficiency (CD4 cell count <200 cells/ $\mu$ L), and it is more likely to be extensive and chronic in immunodeficient patients. Up to one-third of cases may be asymptomatic, although most have fever, headache and nasal discharge. A minority have facial pain and tenderness. Sinusitis should be considered in the differential diagnosis of headache and fever in people with HIV infection.

Most cases of sinusitis in people with HIV are caused by bacterial respiratory pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, although *Pseudomonas aeruginosa* and *Staphylococcus aureus* may also be causative agents. *Mycobacteria* spp., CMV, *Encephalitozoon* spp., *Cryptococcus* spp., *Aspergillus* spp., *Acanthamoeba* spp. *Cryptosporidia* spp. and *Pneumocystis jirovecii* have all been reported as pathogens in people with HIV.<sup>2,3,4</sup> Non-Hodgkin's lymphoma also may affect the sinuses (Table 14.4).<sup>5</sup>

Computed tomography (CT) is the most sensitive imaging modality. The presence of bony erosions on CT scan or ophthalmoplegia suggests possible infection with *Aspergillus* spp., and mandates the need for biopsy.<sup>6</sup> Erosions may also be associated with *Pseudomonas* infection or lymphoma. Opportunistic pathogens need to be considered in the differential diagnosis, and a diagnostic aspirate should be performed in immunodeficient patients and in patients who have a poor response to therapy or severe disease. Samples should be examined for bacteria, fungi, mycobacteria and *microsporidia*.

Standard therapy with antibacterial agents (e.g. amoxicillin with clavulanic acid), decongestant and expectorant agents is appropriate in most cases. In severe cases where parenteral therapy is required, a third-generation cephalosporin (e.g. ceftriaxone) is recommended. In non-responsive disease, broadening of the antimicrobial spectrum to cover *Ps. aeruginosa* and *S. aureus* should be considered, pending results of sinus sampling. Surgery should be considered in the presence of ocular complications, systemic disease not responding

Table 14.4 Causes of sinusitis

Bacterial	Fungal	Protozoan	Viral
<i>Streptococcus pneumoniae</i>	<i>Aspergillus</i> spp.	<i>Encephalitozoon</i> spp.	Cytomegalovirus
<i>Haemophilus influenzae</i>	<i>Cryptococcus</i> spp.	<i>Acanthamoeba</i> spp.	
<i>Staphylococcus aureus</i>		<i>Cryptosporidium parvum</i>	
<i>Pseudomonas aeruginosa</i>		<i>Pneumocystis jirovecii</i>	
<i>Mycobacteria</i> spp.			

to empirical antimicrobial therapy, and in conjunction with antifungal agents in fungal sinusitis. Surgical intervention for infective sinusitis is as effective in people with HIV as in those without HIV.<sup>7</sup>

### 14.3.2 Chronic airflow limitation

Abnormalities of pulmonary parenchyma, including emphysema, airways disease and reduced pulmonary diffusing capacity, occur at a higher incidence in the setting of HIV infection.<sup>8,9</sup> There is an association between cigarette smoking and accelerated emphysema in people with HIV not receiving cART. Half of the smokers with HIV (with a smoking history of  $\geq 25$  pack-years) had radiological evidence of emphysema compared with none of the controls without HIV.<sup>8</sup> Emphysema may be associated with CD8 lymphocyte-mediated damage.

Several studies have demonstrated a reduction in pulmonary diffusing capacity in people with HIV, and that these changes are not predictive of an opportunistic infection in asymptomatic people.<sup>10,11,12</sup> It is possible that these changes are a marker of early emphysema.<sup>13</sup> The relevance of these findings in the cART era is unclear, although smoking cessation is still recommended. There are no data on HIV-specific therapies for airways disease.

### 14.3.3 Lymphocytic interstitial pneumonitis

Lymphocytic interstitial pneumonitis is a clinical condition characterised by cough, dyspnoea, hypoxaemia and a predominantly CD8 lymphocytic infiltrate in the lung.<sup>14</sup> Physical examination reveals crackles. The condition is predominantly seen in children with HIV infection and is rare in adults. Radiographical findings include diffuse reticular or nodular pulmonary infiltrates, and pleural effusions or hilar masses occur infrequently. In some cases, this disorder is part of a multisystem condition known as diffuse infiltrative CD8 lymphocytosis syndrome, which features universal parotid involvement and possible muscle and liver involvement.<sup>15,16</sup> Host genetics appear to play a role in the development of this syndrome, with HLA-DR5 being over represented.<sup>15,16</sup> Although controlled trials are lacking, corticosteroids benefit some patients.<sup>15,16</sup> One atypical case of lymphocytic interstitial pneumonitis (with clubbing) responded to a triple nucleoside antiretroviral regimen.<sup>17</sup>

### Lung malignancy

The incidence of Kaposi's sarcoma (KS) has significantly declined since the introduction of combination antiretroviral therapy (cART). Patients with pulmonary KS usually have advanced immunodeficiency (CD4 cell counts  $< 50$  cells/ $\mu$ L) and present with dry cough and dyspnoea. Half complain of chest pain and one third have haemoptysis, while a minority have fever. Most (85%) will have concomitant skin involvement. Chest x-ray findings consist of diffuse interstitial infiltrates (90%), pleural effusions (80%) and nodules (37%). Diagnosis is made by the characteristic appearance of purple nodules on bronchoscopy, or a bloody pleural effusion. Cytology of sputum is not helpful, but transbronchial biopsy may be. Open lung biopsy is often required for definitive diagnosis. Treatment with liposomal doxorubicin and effective cART has markedly improved the median survival for patients with pulmonary KS.<sup>18</sup>

Non-Hodgkin's lymphoma and Castleman's disease can also present with respiratory symptoms and signs including cough

and dyspnoea, pulmonary nodules and mediastinal and thoracic lymphadenopathy. Primary effusion lymphoma is related to human herpesvirus 8 (HHV8) (as are KS and Castleman's disease). Severely immunodeficient patients usually present with dyspnoea and a pleural effusion, and diagnosis is made by cytology of pleural fluid or pleural biopsy. Prognosis is very poor, despite treatment with chemotherapy and cART.

### Carcinoma of the lung

The risk of lung cancer is three- to six-fold higher in patients with HIV compared with the general population. It is unclear how much of this increased relative risk is due to the higher rates of smoking in HIV populations and what contribution HIV makes. Carcinoma of the lung occurs at any CD4 cell count, and the relationship between immune status and the incidence of non-AIDS-related malignancy is unclear.<sup>18</sup> A trend towards a three-fold increased risk of lung cancer in the antiretroviral treatment interruption arm of the SMART study suggests control of HIV infection with cART may reduce the incidence of this malignancy; however the study was not powered for uncommon events and was stopped early by the study's Data Safety Monitoring Board.<sup>19</sup> Treatment for carcinoma of the lung in people with HIV is no different to that in the general population.

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