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Colonization and aspiration

Secretions in the upper airways of intubated patients often pool above the endotracheal tube. Efforts to reduce the aspiration of these secretions into the lower airways include continuous suction of subglottic secretions through the use of specially designed endotracheal tubes. A meta-analysis of 13 randomized controlled trials including 2442 patients found that subglottic suctioning was associated with lower rates of VAP but with no reduction in mortality.

Aspiration of gastric contents occurs more commonly in patients nursed supine compared to patients nursed in a semi-recumbent position. In intubated patients, some evidence indicates that elevation of the head of the bed to 45 degrees significantly reduces rates of VAP compared to the supine position, but achieving constant head elevation above 30 degrees is practically challenging.

Silver-coated endotracheal tubes have been shown to reduce rates of VAP but are expensive. Other coating materials such as chlorhexidine are also being evaluated.

Decolonisation of the digestive tract

Selective digestive tract decontamination and selective oropharyngeal decontamination are approaches in which antibiotic therapy is used to eradicate potentially pathogenic microorganisms in the oropharynx and gastric tract. In a large study involving 13 ICUs in the Netherlands, 28-day mortality was reduced by 3.5% with the former and 2.9% with the latter. However, a follow-up study reported that bacterial resistance had increased in the ICUs that used decontamination. Hence any strategy that embraces widespread use of antibiotics must also consider the potential harms from increasing antibiotic resistance rates.

Oral decontamination with chlorhexidine is associated with reduced rates of VAP in patients undergoing cardiac surgery; 2% chlorhexidine is more effective than 0.2% or 0.12%. A reduction in mortality as a consequence of oral decontamination strategies has not been confirmed.

Controversies/future developments

Hospital-acquired pneumonia occurring in the non-ICU setting remains a vastly understudied subject. Extrapolating treatment strategies from data derived from VAP may not be acceptable in future as concerns regarding antibiotic stewardship increase. Hurdles related to the diagnosis of VAP remain significant. The incorporation of biomarkers into diagnostic and prognostic algorithms is being actively pursued and holds promise.

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18.4.4 Mycobacteria

Hannah Jarvis and Onn Min Kon

ESSENTIALS

Mycobacteria are gram-negative, rod-shaped bacilli comprising the *Mycobacterium tuberculosis* complex (TB) and nontuberculous mycobacteria.

Tuberculosis

Infection, usually via inhalation, is often asymptomatic but can lead to primary TB or to latent TB infection which can subsequently develop into 'reactivation' or 'post-primary' active disease. Pulmonary TB is the commonest manifestation, but extrapulmonary disease can affect almost any organ. Definitive diagnosis is by culture. Standard chemotherapy involves the use of rifampicin, isoniazid, pyrazinamide, and ethambutol. Drug resistance is an increasing problem. Around 1.3 million people die from TB each year.

Nontuberculous mycobacteria

Infection tends to present with a worsening of chronic respiratory symptoms in patients with underlying lung diseases. Diagnosis is difficult because these organisms are common in the environment. A long course of treatment with several drugs is required.

Introduction

The mycobacteria genus are gram-negative, rod-shaped bacilli which comprise the *Mycobacterium tuberculosis* complex (*M. tuberculosis, M. africanum, M. bovis, M. microti*) and nontuberculous mycobacterium species, the most important of which for human disease include *M. avium* complex, *M. kansasii, M. xenopi, M. fortuitum, M. abscessus*, and *M. malmoense*.

Tuberculosis (TB), the airborne condition caused by infection with the *Mycobacterium tuberculosis* complex, is responsible for more deaths worldwide than any other airborne respiratory infection, with an estimated 10 million incident cases of tuberculosis worldwide and an estimated 1.3 million deaths in 2017. Most of these cases were found in India, China, and South-East Asia, yet TB remains a global disease with just under 6000 cases diagnosed in England in 2017. It also causes significant extrapulmonary disease. The nontuberculous mycobacteria (or 'atypical' mycobacteria) are generally less pathogenic and highly prevalent in the environment, but can cause significant pulmonary, as well as bone or soft tissue disease, in those who are immunocompromised or with existing structural pulmonary conditions.

The emergence of drug-resistant tuberculosis is an increasing concern. Multidrug resistant TB (MDR-TB) is defined as resistance to rifampicin and isoniazid, whereas extensively drug-resistant TB (XDR-TB) is MDR-TB with additional resistance to a fluoroquinolone and at least one of three injectable second-line drugs.

Natural history

Infection is usually via inhalation of aerosolized droplets containing bacilli to the middle or lower lobes. Here activation of the innate immune system results in either complete clearance of the bacilli or primary infection within the lung and associated mediastinal nodes (the Ghon complex). Primary infection is often asymptomatic. Possible outcomes following exposure to *Mycobacterium tuberculosis* complex are shown in Fig. 18.4.4.1.

Latent TB is a term denoting infection which has been contained in a state whereby the bacilli persist in a dormant form, not causing symptoms/disease, but maintaining the potential to reactivate, replicate, and cause pathology at a later stage. Approximately 10–15% of individuals with latent infection go on to develop active TB disease. Individuals that develop disease within 2 years of the initial infection have 'primary' disease, and those who develop disease later (possibly many decades later) have 'post-primary' or 'reactivation' disease. Factors that increase the risk of progression to disease include HIV and immunosuppressive states, including treatments used in transplantation and inflammatory conditions (Table 18.4.4.1).

Table 18.4.4.1 Individuals at high risk for the development of active tuberculosis disease from latent infection (based on NICE guidance)

High-risk groups for development of active TB disease
HIV positive
Injecting drug users
Solid organ transplant recipients
Patients with a haematological malignancy
Patients with chronic renal failure or on haemodialysis
Patients with a previous gastrectomy
Patients receiving antitumour necrosis factor-α streatment
Patients with silicosis

Clinical features

Pulmonary tuberculosis

The manifestation of primary disease in the chest normally consists of mediastinal lymphadenopathy or effusions, although there may be consolidation or collapse secondary to bronchial compression from nodes. Post-primary pulmonary disease classically causes cavitation and 'fluffy' upper zone disease. TB is generally 'subacute' and can cause prolonged symptoms of cough, fever, night sweats, weight loss, and fatigue. Although the cough is initially nonproductive, this generally progresses to sputum production and occasionally

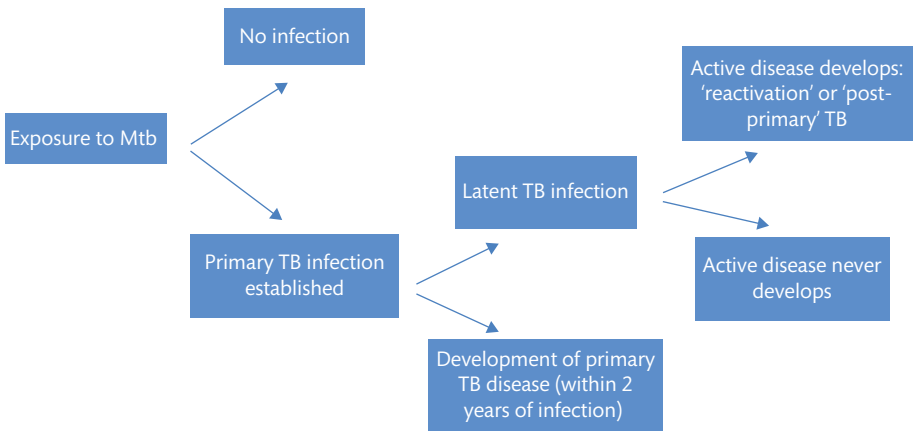

Fig. 18.4.4.1 Outcomes following *Mycobacterium tuberculosis* complex (Mtb) exposure.

haemoptysis. There can also be immune-mediated manifestations including erythema nodosum and uveitis in the absence of obvious clinical disease.

Extrapulmonary tuberculosis

The symptoms and signs of extrapulmonary disease reflect the site of disease as well as the systemic features of general malaise seen in classical pulmonary disease. Common extrapulmonary TB sites are as follows:

- Lymph nodes: The commonest extrapulmonary site is cervical, presenting as fluctuant, tender swellings, often in the supraclavicular or anterior cervical chain. Other common sites include the mediastinum, abdomen, axillary, and inguinal areas.
- Bone: The spine is the commonest site of bony infection (Pott's disease) and destruction at the site of disease can result in pain, deformity, and nerve impingement.
- Gastrointestinal: This classically affects the terminal ileum and can be confused with inflammatory bowel disease. Advanced disease involving the peritoneum can present with ascites.
- Genitourinary tract: This should be considered in patients with a persistent sterile pyuria. Untreated, there is the potential for fibrosis, calcification, and stricture formation.
- Central nervous system: Meningeal or cerebral involvement is rare but should be considered in individuals presenting with headaches, fever, cranial nerve abnormalities, seizures, or behavioural changes. Cerebrospinal fluid obtained from a lumbar puncture may be lymphocytic with high protein and low glucose.
- Miliary tuberculosis: This is a state of disseminated disease with multiorgan involvement that results from haematogenous spread, often in in the young and those with immunocompromise. Without treatment there is rapid progression and a significant risk of death. Pulmonary involvement is common with diffuse, small 'millet-sized' tubercles present throughout the lung fields, but other commonly affected organs can include the brain, bone marrow, abdomen, liver, spleen, and renal tract.

Nontuberculous ('atypical') mycobacteria

Infection tends to present with a worsening of chronic respiratory symptoms in patients with underlying lung diseases such as chronic obstructive pulmonary disease or bronchiectasis. It is also an important pathogen in patients with immunocompromise, particularly HIV. Patients may have systemic features such as weight loss or night sweats, or a worsening of cough and breathlessness. The respiratory radiology of nontuberculous mycobacteria can include cavities, bronchiectasis, small airway inflammation, nodules, and mediastinal nodes

Diagnosis

Mycobacterium tuberculosis complex

The gold standard for diagnosis remains culture of the organism, allowing not only for certainty of diagnosis but also the identification of drug susceptibility. Unfortunately, due to the difficulty of accessing tissue or fluid samples in some instances, as well as the fastidious nature of the pathogen, this is only achieved in approximately 60% of cases. A diagnosis may therefore have to rely on recognition of a combination of clinical features.

Microbiology

A range of samples can be sent for microbiological examination. In pulmonary disease at least three sputum samples should be obtained, using hypertonic saline to induce sputum, if needed. In some patients bronchoscopy may be required to obtain respiratory samples. Samples should be assessed by an auramine or Ziehl–Neelsen stain ('smear'), looking for the presence of acid and alcohol fast bacilli, and also cultured for a minimum of 6 weeks. Molecular techniques such as the polymerase chain reaction are increasingly being used as they can provide a rapid and specific diagnosis. In respiratory samples there is a higher sensitivity than the smear, and molecular testing also allows for the rapid identification of drug resistance.

In extrapulmonary disease samples such as lymph node aspirates, pleural fluid/biopsies, ascites, and cerebrospinal fluid should be sent as appropriate.

Radiology

The classical features of TB are upper zone consolidation with cavitation (Fig. 18.4.4.2), but a range of appearances can be seen on plain imaging, including consolidation, mediastinal lymphadenopathy, and effusions, and in some cases no abnormalities are present. Atypical features are particularly common in older people or immunocompromised and there should be a low threshold for the consideration of CT imaging of the appropriate system in suspected cases. CT allows the identification of intrathoracic abnormalities such as cavities, mediastinal nodes, effusions, and small airway inflammation (Fig. 18.4.4.3), but also importantly in extrapulmonary

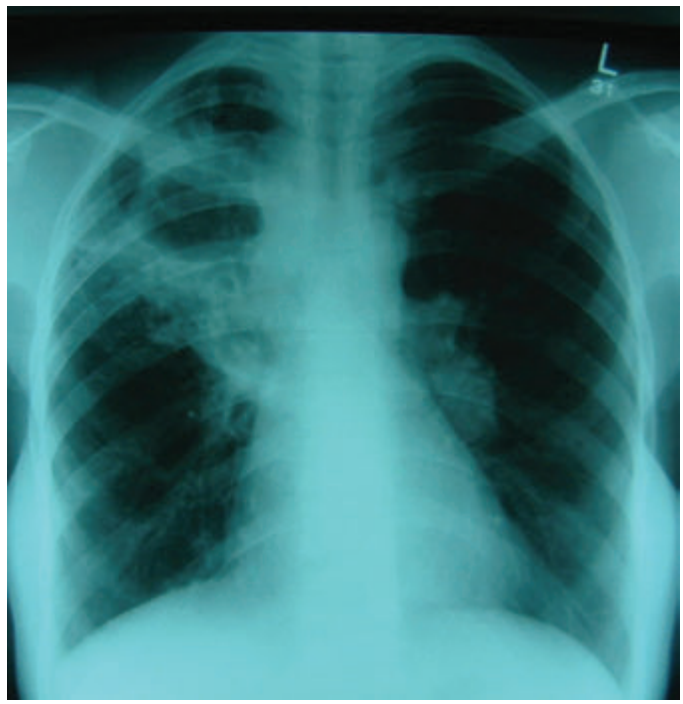

Fig. 18.4.4.2 Chest X-ray showing right upper zone cavitation and consolidation.

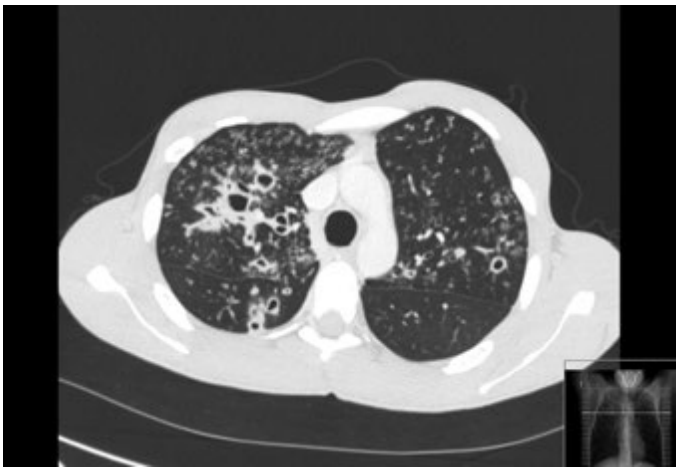

Fig. 18.4.4.3 CT chest showing consolidation with cavitation and bronchiolar ('tree-in-bud') changes.

disease, can help target subsequent investigations to increase the likelihood of successful microbiological sampling. MRI is particularly useful in central nervous system disease. PET/CT scanning may also have a role in identifying occult sites of disease.

Histology/cytology

When tissue has been collected operatively or endoscopically, histological or cytological examination may reveal granulomas. The presence of granulomas, while not specific to mycobacteria, can add significant support to a diagnosis and is useful in excluding other conditions such as malignancy (Fig. 18.4.4.4).

Tuberculin skin test

The intradermal injection of tuberculin, an extract from the filtrate of attenuated *Mycobacterium tuberculosis* complex, causes a delayed hypersensitivity reaction in individuals previously exposed to mycobacteria. This reaction has been used as a surrogate marker for TB infection (latent or active) for over 100 years. A measurement of skin induration is made at 48–72 hours (Fig. 18.4.4.5), but it must be recognized that the skin test can be affected by immunosuppression and patients with advanced disease can even be anergic.

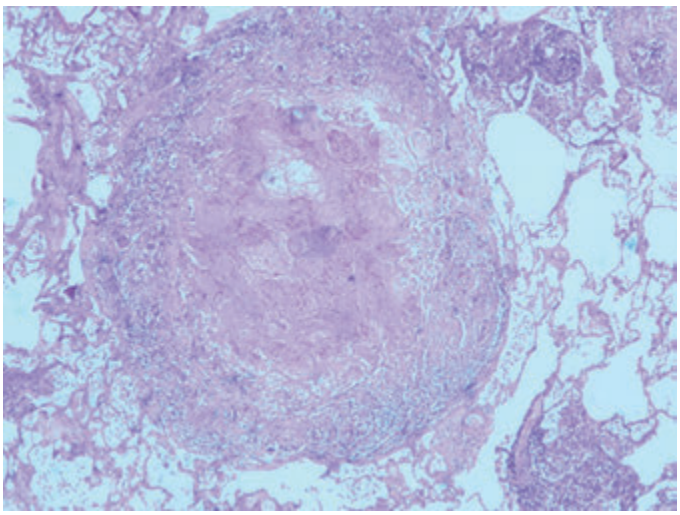

Fig. 18.4.4.4 Granuloma in a lung biopsy specimen.

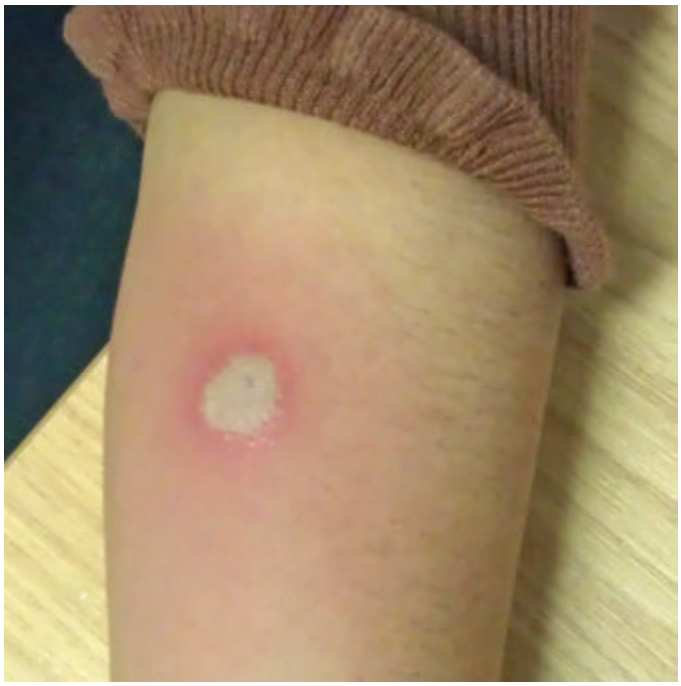

Fig. 18.4.4.5 Positive tuberculin skin test with blistering reaction.

Interferon-γ release assays

Interferon-γ release assays (IGRAs) are peripheral blood assays of prior TB exposure and measure ex-vivo interferon-γ release on stimulation by two specific *Mycobacterium tuberculosis* complex antigens (ESAT-6 and CFP-10). These are relatively specific for *Mycobacterium tuberculosis* complex and avoid any cross reaction with Bacille Calmette–Guérin (BCG) vaccinated individuals (as can be seen in the tuberculin skin test). Although they are likely to be more sensitive than the skin test in immunocompromised individuals, they can still be attenuated in these circumstances. They have the additional advantage of requiring only one patient attendance compared to the two needed for the skin test.

Nontuberculous ('atypical') mycobacterial infection

The diagnosis of clinically significant nontuberculous mycobacterial infection is complex. The environmental prevalence of these pathogens means that repeated culture or a single culture from a sterile site alongside appropriate symptomatology and radiological findings is necessary to make a diagnosis. This is particularly an issue in individuals with chronic lung disease, although in immunocompromised individuals mycobacteria avium complex can also cause significant extrapulmonary disease. The decision to initiate complex and prolonged therapy is often complicated by patient frailty and comorbidities and can have a poor outcome.

Latent tuberculosis

The diagnosis of latent infection (versus active disease) relies on the presence of a positive IGRA or skin test, in the absence of clinical and radiological evidence of active disease.

Table 18.4.4.2 Treatment regimen for latent TB

Drug	Dose and frequency	Duration	Comment
Isoniazid	300 mg OD (5 mg/kg for adults or 10 mg/kg for children)	6 months	NICE WHO
Isoniazid	300 mg OD (5 mg/kg for adults or 10 mg/kg for children) or 900 mg twice weekly (DOT)	9 months	WHO ATS/CDC
Rifampicin	600 mg OD (10 mg/kg)	3–4 months	ATS/CDC WHO
Rifampicin + Isoniazid	600 mg (10 mg/kg) + 300 mg (5 mg/kg adults and 10 mg/kg children) OD	3 months	NICE WHO
Rifapentine + Isoniazid	By body weight + 900 mg (15 mg/kg) once weekly	3 months	ATS/CDC WHO Not in pregnancy or children <2 years

ATS, American Thoracic Society; CDC, Centers for Communicable Disease (USA); DOT, directly observed therapy; WHO, World Health Organization; NICE, National Institute for Clinical Excellence (UK).

Management/treatment

General management

Those with significant pulmonary disease who are productive of sputum, and especially those with confirmed smear positive pulmonary tuberculosis, pose an infectivity risk. These patients should be nursed in respiratory isolation if admitted to hospital, or alternatively self-isolate at home. Repeated sputum smears can guide clinicians in assessing infectivity and response to treatment.

As HIV is a major risk factor for progression from latent infection to disease, and given that treatment of known HIV disease is an important factor in response to treatment, it is important to test for HIV in all cases of active TB.

An assessment should be made of the ability of each patient to comply with their medication regime and directly observed therapy offered for those who may find this difficult (e.g. those who are homeless or engage in substance abuse). The medication regimen can be adjusted so treatment is given on an intermittent basis to assist with this but is not recommended for pulmonary disease as associated with poorer outcomes.

Identification and screening of close contacts should also be undertaken, and preventative treatment offered where appropriate.

Drug treatment

Tuberculosis

Standard antituberculosis chemotherapy involves the use of rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 months, followed by rifampicin and isoniazid for a further four months. The use of multiple agents aims to prevent drug resistance. By two months most cultures should be complete and drug susceptibility available to guide ongoing therapy.

Extrapulmonary tuberculosis is treated with the same regime, although CNS disease requires more prolonged treatment. The use of adjuvant corticosteroids should be considered when starting treatment for CNS or pericardial disease.

Second- and third-line drugs are reserved for cases of drug resistance or intolerance due to their reduced potency and increased toxicity. These drugs include fluoroquinolones such as moxifloxacin or levofloxacin, linezolid, clofazimine and injectable drugs (amikacin/kanamycin or capreomycin). Novel agents such as bedaquiline and delamanid are now available for and notably bedaquiline is recommended as an integral part of the first line therapy in MDR TB.

Latent TB preventative treatment (Table 18.4.4.2) is generally offered to individuals with history of recent exposure and to those who are immunosuppressed, including people about to start treatment with biological agents such as anti-TNF therapy or transplantation candidates.

Atypical mycobacteria

These require treatment with at least two to three agents for 12–24 months depending on the species and clinical presentation (Table 18.4.4.3).

Monitoring

Careful monitoring of patients receiving treatment for TB or atypical mycobacteria is needed to identify the development of potential side effects. The most common of these is drug induced liver damage, which can be severe and, in rare cases, life-threatening. In addition, visual acuity and colour vision testing should be performed due to the potential of ocular complications with ethambutol. Neuropathy from isoniazid can be prevented with the concomitant use of pyridoxine. Drug interactions are common with rifampicin.

Table 18.4.4.3 Suggested treatment regimen for atypical mycobacterial pulmonary infections in HIV negative patients (based on American and British Thoracic Societies' guidance)

Pathogen	Drug regime	Duration
M. *avium* complex	Clarithromycin or azithromycin + rifampicin + ethambutol (+/- streptomycin/amikacin if advanced disease or cavities)	Until 12 months of negative sputa
M. *kansasii*	Rifampicin + ethambutol + isoniazid or a macrolide (clarithromycin/azithromycin)	Until 12 months of negative sputa
M. *xenopi*	Clarithromycin or azithromycin + rifampicin + ethambutol + either a quinolone or isoniazid	Until 12 months of negative sputa
M. *abscessus*	A multidrug regime involving and induction and continuation phase with combinations of injectable, oral and nebulised antibiotics	Variable

Prevention

The World Health Organization has prioritized the eradication of tuberculosis and set the goal of reducing the incidence of TB to less than one per million population by 2050 in their STOP TB campaign. This requires commitment to finding and treating active cases of tuberculosis, and also to identifying latent infection. Improving socioeconomic conditions is vital in reducing transmission. There are ongoing studies of new treatments and vaccinations, but the only available vaccine currently is the BCG, which has limited evidence for effectiveness, protecting mainly against miliary disease and meningitis in children.

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18.4.5 Pulmonary complications of HIV infection

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ESSENTIALS

Most HIV-positive individuals will experience at least one significant episode of pulmonary disease during their lifetime. The immune status of the HIV-infected patient is the primary determinant of the risk of developing specific pulmonary diseases: those with advanced immunosuppression are predisposed to opportunistic infections and malignancies; those with mild or no immunosuppression are at greater risk of conditions including community-acquired pneumonia, chronic obstructive pulmonary disease, pulmonary hypertension, and interstitial lung disease.

Pulmonary infections related to HIV infection with severe immunosuppression include: (1) *Pneumocystis jirovecii* pneumonia—typically presents with gradual onset of breathlessness and dry cough, and a chest X-ray showing diffuse bilateral infiltrates. Diagnosis requires direct visualization of fungal spores in respiratory secretions. First-line treatment is with high-dose trimethoprim/sulfamethoxazole. (2) Tuberculosis—is the leading cause of death among people with HIV. Presentation may be nonspecific and atypical, and tissue biopsy may be required for diagnosis. Treatment is as for HIV-uninfected patients, but great care is needed regarding drug interactions. (3) Fungal infections including aspergillosis and cryptococcosis.

Lung malignancies related to HIV infection with severe immunosuppression include: (1) Kaposi's sarcoma—caused by human herpesvirus (HHV-8), usually in patients with obvious mucocutaneous lesions and diagnosed by finding of purplish plaques at bronchoscopy; treatment is with systemic chemotherapy. (2) Lymphoma—typically non-Hodgkin's B-cell lymphoma or primary effusion lymphoma (also caused by HHV-8).

Introduction

In 2017, 37 million adults were living with HIV, mostly in Low and Middle Income Countries (LMIC). In many countries it is becoming chronic disease with life expectancies approximating normal due to the use of highly active combination antiretroviral therapy (cART). This is testimony to the fact that the risk of developing an opportunistic infection or malignancy is markedly reduced by being on cART and having an undetectable HIV-1 viral load. Nevertheless, with unequal access to diagnostics, treatment, and education worldwide, 1.8 million people are still infected every year and many develop opportunistic infections and HIV-associated neoplasms leading to almost one million AIDS-related deaths.

The lungs are commonly affected in HIV-positive individuals, 60% of whom will experience at least one significant episode of pulmonary disease during their lifetime. Subsequently, pulmonary disease remains a significant cause of morbidity and mortality. A wide range of conditions can occur, ranging from opportunistic infections and tumours to interstitial lung diseases. Available data suggest that both cellular and humoral lung immunity is impaired in HIV and that alveolar macrophages are an important reservoir for HIV in the lung.

This chapter will concentrate on common causes of HIV-related lung disease and can be divided into:

- HIV disease with mild or no immunosuppression (normal or near normal CD4 counts)—in these patients typical community-acquired infections occur at greater frequency than in the general population, and chronic obstructive pulmonary disease (COPD), pulmonary hypertension, interstitial lung disease, and lung cancers are common, partly related to immune defects and lifestyle factors.
- HIV disease with advanced immunosuppression—in these patients abnormalities of the innate and adaptive lung immunity predispose them to opportunistic infections and opportunistic malignancies.