

EXTRAPULMONARY TUBERCULOSIS

Tuberculosis that affects any organ outside the pulmonary parenchyma is designated extrapulmonary tuberculosis. In addition to all the sites of the body outside the chest affected by tuberculosis that are clearly extrapulmonary, certain forms of tuberculosis occurring in sites that are fully or partially within the chest are also considered extrapulmonary.

Pleural tuberculosis and tuberculosis of the hilar or mediastinal lymph nodes are classified as extrapulmonary, provided there are no discernible lung parenchymal abnormalities.

Tuberculous meningoencephalitis – risk factors and clinical features. Lumbar puncture and examination of the cerebrospinal fluid. Cerebral tuberculoma - clinical aspects, course and prognosis.

Tuberculous Meningitis and Tuberculoma

Tuberculosis of the central nervous system (CNS) is seen most often in young children but also develops in adults, especially those infected with HIV. Tuberculous meningitis results from the hematogenous spread of primary or postprimary pulmonary disease or from the rupture of a subependymal tubercle into the subarachnoid space. In more than half of cases, evidence of old pulmonary lesions or a miliary pattern is found on chest radiography. The disease often presents subtly as headache and slight mental changes after a prodrome of weeks of low-grade fever, malaise, anorexia, and irritability. If not recognized, tuberculous meningitis may evolve acutely with severe headache, confusion, lethargy, altered sensorium, and neck rigidity. Typically, the disease evolves over 1–2 weeks, a course longer than that of bacterial meningitis. Paresis of cranial nerves (ocular nerves in particular) is a frequent finding, and the involvement of cerebral arteries may produce focal ischemia. The ultimate evolution is toward coma, with hydrocephalus and intracranial hypertension.

Lumbar puncture is the cornerstone of diagnosis. In general, examination of the cerebrospinal fluid (CSF) reveals a high leukocyte count (up to 1000/L), usually with a predominance of lymphocytes but sometimes with a predominance of neutrophils in the early stage; a protein content of 1–8 g/L (100–800 mg/dL); and a low glucose concentration. However, any of these three parameters can be within the normal range. AFB are seen on direct smear of CSF sediment in up to one-third of cases, but repeated lumbar punctures increase the yield. Culture of CSF is diagnostic in up to 80% of cases and remains the gold standard. Polymerase chain reaction (PCR) has a sensitivity of up to 80%, but rates of false-positivity reach 10%. The ADA concentration may be a sensitive test but has low specificity.

Imaging studies (CT and MRI) may show hydrocephalus and abnormal enhancement of basal cisterns or ependyma.

If unrecognized, tuberculous meningitis is uniformly fatal. This disease responds to chemotherapy; however, neurologic sequelae are documented in 25% of treated cases, in most of which the diagnosis has been delayed. Clinical trials have demonstrated that patients given adjunctive glucocorticoids may experience faster resolution of CSF abnormalities and elevated CSF pressure. In a recent study, adjunctive dexamethasone (0.4 mg/kg per day given IV and tapering by 0.1 mg/kg per week until the fourth week, when 0.1 mg/kg per day was administered; followed by 4 mg/d given by mouth and tapering by 1 mg per week until the fourth week, when 1 mg/d was administered) significantly enhanced the chances of survival among persons >14 years of age but did not reduce the frequency of neurologic sequelae.

Tuberculoma, an uncommon manifestation of CNS tuberculosis, presents as one or more space-occupying lesions and usually causes seizures and focal signs. CT or MRI reveals contrast-enhanced ring lesions, but biopsy is necessary to establish the diagnosis.

Pleural tuberculosis - pathogenesis and clinical aspects. Physical signs and radiographic features. Thoracentesis examination of the pleural fluid. Tuberculosis of the upper airways. Indication for bronchoscopy.

Pleural Tuberculosis

Involvement of the pleura is common in primary tuberculosis and may result from either contiguous spread of parenchymal inflammation or, as in many cases of pleurisy accompanying postprimary disease, actual penetration by tubercle bacilli into the pleural space. Depending on the extent of reactivity, the effusion may be small, remain unnoticed, and resolve spontaneously or may be sufficiently large to cause symptoms such as fever, pleuritic chest pain, and dyspnea. Physical findings are those of pleural effusion: dullness to percussion and absence of breath sounds. A chest radiograph reveals the effusion and, in up to one-third of cases, also shows a parenchymal lesion.

Thoracentesis is required to ascertain the nature of the effusion and to differentiate it from manifestations of other etiologies. The fluid is straw-colored and at times hemorrhagic; it is an exudate with a protein concentration >50% of that in serum (usually ~4–6 g/dL), a normal to low glucose concentration, a pH of ~7.3 (occasionally <7.2), and detectable white blood cells (usually 500–6000/L). Neutrophils may predominate in the early stage, while mononuclear cells are the typical finding later. Mesothelial cells are generally rare or absent. AFB are seen on direct smear in only 10–25% of cases, but cultures may be positive for M.

tuberculosis in 25–75% of cases; positive cultures are more common among postprimary cases. Determination of the pleural concentration of adenosine deaminase (ADA) is a useful screening test: tuberculosis is virtually excluded if the value is very low. Needle biopsy of the pleura is often required for diagnosis and reveals granulomas and/or yields a positive culture in up to 80% of cases. This form of pleural tuberculosis responds well to chemotherapy and may resolve spontaneously. The usefulness of glucocorticoid administration is doubtful.

Tuberculosis of the Upper Airways

Nearly always a complication of advanced cavitary pulmonary tuberculosis, tuberculosis of the upper airways may involve the larynx, pharynx, and epiglottis. Symptoms include hoarseness, dysphonia, and dysphagia in addition to chronic productive cough. Findings depend on the site of involvement, and ulcerations may be seen on laryngoscopy. Acid-fast smear of the sputum is often positive, but biopsy may be necessary in some cases to establish the diagnosis. Carcinoma of the larynx may have similar features but is usually painless.

Peripheral lymph node TB. Genitourinary and genital TB. Skeletal tuberculosis. Less common extrapulmonary forms (gastrointestinal tuberculosis, tuberculous pericarditis and other).

Lymph-node tuberculosis (tuberculous lymphadenitis)

This form of tuberculosis, which occurs relatively early after primary infection with *Mycobacterium tuberculosis*, often affects young people in countries with a high prevalence of tuberculosis.

Lymph-node tuberculosis presents as painless swelling of the lymph nodes, most commonly at posterior cervical and supraclavicular sites (a condition historically referred to as scrofula). Lymph nodes are usually discrete and nontender in early disease but may be inflamed and have a fistulous tract draining caseous material. Associated pulmonary disease is seen in >40% of cases. Systemic symptoms are usually limited to HIV-infected patients. The diagnosis is established only by fine-needle aspiration or surgical biopsy. AFB are seen in up to 50% of cases, cultures are positive in 70–80%, and histologic examination shows granulomatous lesions.

Differential diagnosis includes a variety of infectious conditions, neoplastic diseases such as lymphomas or metastatic carcinomas.

Genitourinary Tuberculosis

Genitourinary tuberculosis may involve any portion of the genitourinary tract. Local symptoms predominate, and up to one-third of patients may concomitantly

have pulmonary disease. Urinary frequency, dysuria, nycturia, hematuria, and flank or abdominal pain are the common presentations. However, patients may be asymptomatic and the disease discovered only after severe destructive lesions of the kidneys have developed. Urinalysis gives abnormal results in 90% of cases, revealing pyuria and hematuria. The documentation of culture-negative pyuria in acidic urine raises the suspicion of tuberculosis. Intravenous pyelography, abdominal CT, or MRI may show deformities and obstructions, and calcifications and ureteral strictures are suggestive findings. Culture of three morning urine specimens yields a definitive diagnosis in nearly 90% of cases. Severe ureteral strictures may lead to hydronephrosis and renal damage.

Genital tuberculosis is diagnosed more commonly in female than in male patients. In female patients, it affects the fallopian tubes and the endometrium and may cause infertility, pelvic pain, and menstrual abnormalities. Diagnosis requires biopsy or culture of specimens obtained by dilatation and curettage. In male patients, tuberculosis preferentially affects the epididymis, producing a slightly tender mass that may drain externally through a fistulous tract; orchitis and prostatitis may also develop. In almost half of cases of genitourinary tuberculosis, urinary tract disease is also present. Genitourinary tuberculosis responds well to chemotherapy.

Skeletal Tuberculosis

In bone and joint disease, pathogenesis is related to reactivation of hematogenous foci or to spread from adjacent paravertebral lymph nodes. Weight-bearing joints (the spine in 40% of cases, the hips in 13%, and the knees in 10%) are most commonly affected. Spinal tuberculosis (Pott's disease or tuberculous spondylitis) often involves two or more adjacent vertebral bodies. While the upper thoracic spine is the most common site of spinal tuberculosis in children, the lower thoracic and upper lumbar vertebrae are usually affected in adults. From the anterior superior or inferior angle of the vertebral body, the lesion slowly reaches the adjacent body, later affecting the intervertebral disk. With advanced disease, collapse of vertebral bodies results in kyphosis (gibbus). A paravertebral «cold» abscess may also form. In the upper spine, this abscess may track to and penetrate the chest wall, presenting as a soft tissue mass; in the lower spine, it may reach the inguinal ligaments or present as a psoas abscess. CT or MRI reveals the characteristic lesion and suggests its etiology.

The differential diagnosis includes tumors and other infections. Pyogenic bacterial osteomyelitis, in particular, involves the disk very early and produces rapid sclerosis. Aspiration of the abscess or bone biopsy confirms the tuberculous etiology, as cultures are usually positive and histologic findings highly typical. A

catastrophic complication of Pott's disease is paraplegia, which is usually due to an abscess or a lesion compressing the spinal cord. Paraparesis due to a large abscess is a medical emergency and requires rapid drainage. Tuberculosis of the hip joints, usually involving the head of the femur, causes pain; tuberculosis of the knee produces pain and swelling. If the disease goes unrecognized, the joints may be destroyed. Diagnosis requires examination of the synovial fluid, which is thick in appearance, with a high protein concentration and a variable cell count. Although synovial fluid culture is positive in a high percentage of cases, synovial biopsy and tissue culture may be necessary to establish the diagnosis. Skeletal tuberculosis responds to chemotherapy, but severe cases may require surgery.

Gastrointestinal Tuberculosis

Gastrointestinal tuberculosis is uncommon. Various pathogenetic mechanisms are involved: swallowing of sputum with direct seeding, hematogenous spread, or (largely in developing areas) ingestion of milk from cows affected by bovine tuberculosis. Although any portion of the gastrointestinal tract may be affected, the terminal ileum and the cecum are the sites most commonly involved. Abdominal pain (at times similar to that associated with appendicitis) and swelling, obstruction, hematochezia, and a palpable mass in the abdomen are common findings at presentation. Fever, weight loss, anorexia, and night sweats are also common. The yield of direct smear and culture is relatively low, biopsy (with a specimen best obtained by laparoscopy) is often needed to establish the diagnosis. In the majority of cases gastrointestinal tuberculosis is one of manifestation of TB generalization.

Less Common Extrapulmonary Forms

Tuberculosis may cause chorioretinitis, uveitis, panophthalmitis, and painful hypersensitivity-related phlyctenular conjunctivitis.

Cutaneous manifestations of tuberculosis include primary infection due to direct inoculation, abscesses and chronic ulcers, scrofuloderma, lupus vulgaris (a smoldering disease with nodules, plaques, and fissures), miliary lesions, and erythema nodosum.

Tuberculous pericarditis develops due to direct progression of a primary focus within the pericardium, to reactivation of a latent focus, or to rupture of an adjacent subcarinal lymph node, pericardial tuberculosis has often been a disease of the elderly in countries with low tuberculosis prevalence but also develops frequently in HIV-infected patients.

Tuberculous otitis is rare and presents as hearing loss, otorrhea, and tympanic membrane perforation.

Adrenal tuberculosis presents as adrenal insufficiency.

These forms also occur as a manifestation of disseminated disease.

TUBERCULOSIS ACCOMPANIED BY OTHER DISEASES AND SPECIAL SITUATIONS.

Tuberculosis and HIV infection. Clinical aspects of HIV-TB. Course and prognosis for tuberculosis depending on stage of HIV-infection.

HIV-Associated Tuberculosis

HIV infection is the most powerful risk factor that increases the likelihood of development of tuberculosis in a person previously infected with *Mycobacterium tuberculosis*. HIV-associated tuberculosis is included in the current international AIDS definition.

The circumstances of diagnosis are variable: tuberculosis may occur in individuals infected with HIV, while at other times it may be diagnosed in individuals whose HIV status is unknown; it is thus frequently the sentinel event that indicates HIV infection.

Cough for more than a month and recurrent pneumonia may be associated with other complications of HIV infection. As recurrent pneumonia due to other pathogens frequently occurs in HIV-infected patients, it should be kept in mind that seropositive patients with respiratory symptoms and abnormalities on chest X-ray should not always be assumed to have tuberculosis, and that the diagnosis of pulmonary tuberculosis should be based on criteria as rigorous as those for seronegative patients. Nevertheless, if a HIV-positive patient has persistent cough, investigations should systematically be made to check for the presence of tuberculosis.

The diagnosis of tuberculosis in HIV-infected patients may be difficult not only because of the increased frequency of sputum-smear negativity (up to 40% in culture-proven pulmonary cases) but also because of atypical radiographic findings, a lack of classic granuloma formation in the late stages, and a negative TST. Delays in treatment may prove fatal.

Clinical aspects

A complex biological interplay occurs between *M. tuberculosis* and HIV in the co-infected host that results in the worsening of both pathologies. HIV promotes progression of *M. tuberculosis* latent infection to disease and, in turn, *M. tuberculosis* enhances HIV replication, accelerating the natural evolution of HIV infection

Tuberculosis can appear at any stage of HIV infection, and its presentation varies with the stage. The clinical features of tuberculosis are closely related to the level of immune deficiency of the HIV-infected patient. In countries with a high prevalence of tuberculosis, tuberculosis is often a very early complication of HIV infection and often occurs when the level of cellular immunity is relatively high. It thus has the same aspects as among HIV-negative individuals.

At an early stage of immune deficiency, when the number of CD4 lymphocytes is greater than 200/mm³, the clinical and radiographic features of pulmonary tuberculosis are similar to those in patients without HIV infection, with a predominance of smear-positive patients (75–85%). Above this level, a complete TB granuloma is produced in response to *M. tuberculosis* infection, including multinucleated giant cells, macrophages, CD4+ and CD8+ T lymphocytes and a central caseous necrosis. Pulmonary tuberculosis in such patients presents in a typical manner, with upper-lobe infiltrates and cavitation and without significant lymphadenopathy or pleural effusion.

At an advanced stage of immune deficiency, when the number of CD4+ lymphocytes is less than 200/mm³, the formation of the granuloma is progressively impaired. Thus the appearance of tuberculosis changes from the typical, localized forms to the atypical, disseminated forms. In late stages of HIV infection, a primary tuberculosis-like pattern is more common. It is characterized by diffuse interstitial or miliary infiltrates, little or no cavitation, associated with mediastinal lymphadenopathy and/or pleurisy. Overall, sputum smears may be positive less frequently among tuberculosis patients with HIV infection than among those without; thus, the diagnosis of tuberculosis may be unusually difficult, especially in view of the variety of HIV-related pulmonary conditions mimicking tuberculosis.

Extrapulmonary tuberculosis is common among HIV-infected patients. In various series, extrapulmonary tuberculosis - alone or in association with pulmonary disease - has been documented in 40–60% of all cases in HIV-co-infected individuals. The most common extrapulmonary localizations of TB are serous effusions (pleurisy, pericarditis, ascites) and lymphadenopathy. Serous effusions (pleural, pericardial and/or peritoneal) are quite frequent in HIV/AIDS patients and may be caused by various other etiological agents. In TB pleurisy, the aspirated fluid is exudative with a predominance of lymphocytes. Pleural biopsy and mycobacterial culture of the fluid are the most useful and specific diagnostic tools. Adenosine deaminase (ADA) levels above 50 U/L in non-purulent pleural fluid specimens have a high positive predictive value for the diagnosis of TB.

Cervical lymphadenitis is the second most frequent extrapulmonary localization of TB in AIDS patients, after pleurisy. Aspiration puncture of a

swollen and fluctuant lymphadenopathy usually yields a purulent or caseous material with abundant AFB on microscopy examination.

Meningitis are also frequent, particularly in advanced HIV disease. Other organs may be involved, including the gastrointestinal tract, liver, kidneys, urinary tract, adrenal gland, larynx and genital (male and female) tract.

Course of tuberculosis

The course of tuberculosis under treatment in HIV-positive patients is similar to that observed in HIV-negative patients, if standardised short-course chemotherapy is applied. However, side-effects are more frequent. The risk of dying is still higher in HIV-infected patients. Much of this is due to other complications of HIV infection but some deaths seem directly due to tuberculosis. The long-term prognosis is therefore poor, as in all HIV-positive patients. But treatment of the patient's tuberculosis and antiretroviral drugs for HIV gives the patient a longer period of improved health. Moreover, anti-tuberculosis treatment stops the spread of tuberculosis to others. Unfortunately, tuberculosis seems to speed up the progress of the HIV illness. In addition to anti-tuberculosis treatment, antiretroviral treatment must thus be offered to all tuberculosis patients known to have HIV infection.

So, tuberculosis is a common complication of HIV infection. It can be the first sign of infection or it can occur in a subject known to be HIV-infected. Patients with HIV or AIDS who present with signs compatible with tuberculosis should undergo the same rigorous investigations as HIV-negative patients. The standardized chemotherapy regimens used for treating tuberculosis are as effective among HIV-positive as among HIV-negative patients; however, the fatality rate is higher among HIV-positive patients because of AIDS-related complications.

Immune reconstitution inflammatory syndrome

This syndrome, also known as IRIS, consists of a paradoxical worsening of clinical disease shortly after the initiation of drug treatment. Irrespective of the HIV status, the immune system is impaired in the advanced stages of TB as shown by low levels of circulating CD4⁺ T lymphocytes. Once the treatment starts to produce an effect, an “immune restoration” occurs that reflects the reconstituted immunity to *M. tuberculosis*. The syndrome includes an enlargement of the affected lymph nodes and of the lung lesions accompanied by an exacerbation of the general symptoms (fever and malaise and/or local reactions in lymph nodes, lungs, pleura and the central nervous system, depending on the localization of the TB lesions). This condition resolves spontaneously during the course of antituberculosis therapy.

Since the beginning of the highly active antiretroviral therapy era, the immune reconstitution inflammatory syndrome has been observed with increasing frequency. This syndrome is observed most frequently when the treatment of both infections is started in close temporal proximity. In AIDS patients, the immune reconstitution inflammatory reactions are best managed with anti-inflammatory agents, including corticosteroids such as prednisone 20-40 mg/d, if necessary. Both antituberculosis and antiretroviral therapy should be continued during the entire reconstitution syndrome.

Treatment of latent tuberculosis infection in HIV/AIDS patients

The classical method for detection of TB infection is the skin test reaction with PPD RT23 2 UT or PPDS 5 UT. In HIV-infected persons, a nodule of 5 mm or more is considered positive. Particularly in this population, the reliability of the method of detection of latent infection is highly dependent on the level of immunosuppression. Quantiferon is a whole blood assay for the detection of interferon gamma produced by peripheral lymphocytes in response to specific *M. tuberculosis* antigens. This test often yields negative or indeterminate results in severely immunosuppressed AIDS patients. On the other hand, preliminary results in AIDS patients suggest that the performance of ELISPOT a test that enumerates *Mycobacterium tuberculosis* antigen-specific IFN- γ -secreting T cells test is not affected by HIV-associated immunosuppression.

When latent TB infection is detected in an HIV-positive person, he/she should receive chemoprophylaxis. The treatment consists of a course of at least six months preferable nine months of INH. Alternatively, a four-month course of RIF may be indicated. Both drugs are administered in their usual dosages.

The risk exists, however, of overlooking a sub-clinical TB, thus selecting INH resistant, or worse, RIF resistant mutants. A two-month course of treatment consisting of two drugs (RIF plus PZA) is expected to prevent the development of resistance, while the short-course treatment would grant a better adherence. The protective effect of a number of TB chemoprophylaxis regimens in HIV-positive, PPD-positive persons has been sufficiently proven.

Chronic bronchitis and COPD

Chronic bronchitis and COPD increase the risk of active TB disease and its unfavorable course. The reasons of that are defects in local defense factors of respiratory system, mucociliary clearance, insufficient aeration and perfusion of defective sections of lung tissue. Comorbidity makes difficult to diagnose TB which leads to late diagnosis. Patients and doctors evaluate increasing symptoms (cough, fever, dyspnea chest pain) as exacerbation of existing non-specific

diseases. All patients with prolonged symptoms of intoxication and cough persisting for more than 3 weeks with sputum, hemoptysis or chest pain should be examined by sputum microscopy.

Diabetes mellitus

Before the advent of anti-tuberculosis chemotherapy and the generalized use of insulin therapy, the incidence and mortality rates of TB among patients with diabetes mellitus were high. In patients whose diabetes is difficult to control, the immune defects are presumably more severe, and pulmonary TB tends to be more aggressive producing cavities and extensive lesions in the lower third of the lungs.

The presence of diabetes mellitus may potentiate the adverse effects of anti-TB drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of DR-TB. The health-care provider should be in close communication with the physician who manages the patient's diabetes. Oral hypoglycaemic agents are not contraindicated during the treatment of DR-TB but may require the patient to increase the dosage. Use of ethionamide or prothionamide may make it more difficult to control insulin levels. Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly thereafter.

Renal insufficiency

In patients with chronic renal insufficiency, TB often has a slow onset with lowgrade fever, dry cough, dyspnea, pleuritis and/or pericarditis. TB occurs frequently in patients undergoing long periods of dialysis (on average, after 22 months), and extrapulmonary presentations (i.e. ganglionar) are common. As the mortality rate is high when the diagnosis is delayed, TB must always be considered a possibility, and appropriate invasive and non-invasive procedures should be employed to ensure an early diagnosis. As a rule, patients with *chronic renal failure* should not receive aminoglycosides and should receive ethambutol only if serum levels can be monitored. Isoniazid, rifampin, and pyrazinamide may be given in the usual doses in cases of mild to moderate renal failure, but the dosages of isoniazid and pyrazinamide should be reduced for all patients with severe renal failure except those undergoing hemodialysis.

Peptic ulcer disease

In patients with peptic ulcer disease – higher risk of developing TB. Frequent exacerbations and digestive disorders at peptic ulcer disease reduce the organism's resistance, promoting the development of TB.

TB in these patients tends to progression, the development chronic forms, long-term exacerbation. The simultaneous presence of two diseases adversely affects their course, there are often complications peptic ulcer disease, massive gastric bleeding, reduces the effectiveness of anti-TB treatment.

During exacerbation peptic ulcer disease anti-TB drugs designate parenterally in combination with anti-ulcer medication. After elimination of exacerbation back to give anti-TB drugs by the generally accepted methods.

Liver disorders

The first-line drugs isoniazid, rifampicin and pyrazinamide are all associated with hepatotoxicity. Of the three, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Pyrazinamide is the most hepatotoxic of the three first-line drugs. Among the second-line drugs, ethionamide, protionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with the fluoroquinolones.

Patients with a history of liver disease can receive the usual DR-TB chemotherapy regimens provided there is no clinical evidence of severe chronic liver disease, hepatitis virus carriage, recent history of acute hepatitis or excessive alcohol consumption. However, hepatotoxic reactions to antituberculosis drugs may be more common in these patients and should be anticipated.

In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped.

Uncommonly, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or antituberculosis treatment. In this case, clinical judgement is necessary. In some cases, it is possible to defer antituberculosis treatment until the acute hepatitis has been resolved. In other cases when it is necessary to treat DR-TB during acute hepatitis, the combination of four nonhepatotoxic drugs is the safest option.

Silicotuberculosis

Silicos is a form of pneumoconiosis. It results from inhalation of dust containing crystalline silica particles of size 0,5-5 microns in diameter. Prevalence of pulmonary TB in silicotics is more common when to prevalence in general population. This entity is called silicotuberculosis.

Silicotic workers have an approximately threefold greater risk of developing TB and a three- to fivefold greater risk of dying from TB than the general population and 20% to 25% develop TB at some time in their working career or

retirement. The association is dose-dependent, increasing with greater profusion of silicosis on chest radiograph, although the size of nodules and presence of progressive massive fibrosis might be more significant in determining the risk of TB.

Mechanisms underlying these associations are complex and not fully understood. However, alveolar macrophages are the first line of defence against mycobacteria and are also required to phagocytose and assist in the clearance of silica particles. The physicochemical properties of crystalline quartz result in damage to cell membranes through a variety of processes, leading to death, lysis and release of dust particles together with potentially tissue-damaging enzymes and other substances.

The onset of symptoms may be insidious, and general symptoms (fever, night sweats, muscle pain and fatigue) predominate. The presence of hemoptysis and increasing respiratory symptoms should alert to the possibility of TB. The presence of silicosis makes chest radiographic changes more difficult to interpret. Careful scrutiny for new changes, particularly the development of cavitation, poorly defined «fluffy» infiltrates surrounding previous tuberculous lesions and the appearance of new crops of poorly defined nodules should be performed. Sputum examination is mandatory and should be repeated in high-risk cases. Chest CT scans may help to define potential new areas of involvement, and serve as a guide to bronchoscopic examination and sampling. A high index of suspicion must be maintained in all silica-exposed and silicotic patients as TB is a frequent finding in postmortem examinations.