Tuberculosis & Sarcoidosis
Document control

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Changes since last version
A. TUBERCULOSIS
Introduction

Definition

*Tuberculosis is a chronic, progressive infection with a period of latency following initial infection. It occurs most commonly in the lungs. Pulmonary symptoms include productive cough, chest pain, and dyspnoea. Diagnosis is by sputum culture and smear. Treatment is with multiple antimicrobial agents.*

Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis, also known as 'the tubercle bacillus'.

TB commonly affects the lungs, but can reach any part of the body.

- It is usually spread by the coughs or sneezes of an infected person, but is not highly contagious.
- Prolonged close contact with a person with TB, for example, living in the same household is usually necessary for infection to be passed on.
- It may take many years before someone infected with TB develops the full disease.

Tuberculosis is a ‘Notifiable Disease’ under the Public Health (Infectious Diseases) Regulations 1988 and must be reported to the Health Protection Agency.
Description

Epidemiology

Tuberculosis (TB) has been identified in human remains more than 9,000 years old.

It is the leading infectious cause of morbidity and mortality in adults worldwide, killing about 2 million people every year.

About 1.6 billion are infected worldwide. Of these, only 15 million have active disease at any given time. Case rates vary widely by country, age, race, sex, and socioeconomic status.

According to WHO figures 26 of the 30 countries with the greatest TB load are in Africa, and many of these have a prevalence 10 times more than the 40 cases per 100,000 per year figure required to qualify as a 'high load country'.

HIV infection is the greatest single medical risk factor because cell-mediated immunity, which is impaired by HIV, is essential for defence against TB; other immunosuppressive illnesses (e.g. diabetes) or therapies (e.g. corticosteroids) are risks but less so than HIV.

TB is still a major problem in many countries. It has been on the increase in the developed world in recent years, probably because of increased air travel and movement of people from areas where it is common.

In the UK from September 2005, a new targeted programme of BCG vaccination was introduced. Only those people at high risk of contracting TB will be vaccinated, as opposed to all school children.

Prevalence

TB worldwide is a massive problem and large numbers die annually. In England cases fell progressively until the mid-1980s but started to rise again in the early 1990s.

In 2006, there were 8497 cases of TB reported in the UK (14.0 per 100,000) and the London region accounted for 40% of cases (44.8 per 100,000). TB is potentially curable with a course of specific antibiotics taken for at least 6 months.

About 8000 new cases of TB are currently reported each year in the United Kingdom. Most cases occur in major cities, particularly in London.

The most important part of controlling TB is identifying and treating those who already have the disease, to shorten their infection and to stop it being passed on to others.
Aetiology

TB properly refers only to disease caused by Mycobacterium tuberculosis (M. tuberculosis).

Similar disease occasionally results from M. bovis, M. africanum, and M. microti.

In the United Kingdom TB occurs almost exclusively from inhalation of droplet nuclei containing M. tuberculosis. They disperse primarily through coughing, singing, and other forced respiratory manoeuvres by a person with active pulmonary disease.

People with cavitating pulmonary lesions are especially infectious. Droplet nuclei containing tubercle bacilli may float on room-air currents for several hours, increasing the chance of spread. About 25% of household contacts acquire infection. Healthcare practitioners who have close contact with active cases have increased risk.

Transmission is enhanced by overcrowding; thus, people living in poverty or in institutions are at particular risk. Once effective treatment begins, however, cough rapidly decreases, and after two weeks, TB is no longer contagious. Fomites (e.g. clothes or bedding) do not appear to facilitate spread.

Pathophysiology

Tubercle bacilli initially produce a primary infection, followed by a latent (dormant) phase and then, in some cases, by active disease. Infection is not transmissible in the primary and latent phases.

Primary infection:

Airborne droplet nuclei lodge in sub-pleural terminal airspaces, predominantly in the lower lung, usually in only one site. Tubercle bacilli replicate inside macrophages, ultimately killing them. Inflammatory cells are attracted to the area, causing a tubercle to form and in some cases pneumonitis. In the early weeks of infection, some infected macrophages are carried to regional lymph nodes (eg, hilar, mediastinal). Haematogenous spread to any part of the body, particularly the apical-posterior portion of the lungs, epiphyses of the long bones, kidneys, vertebral bodies, and meninges, may occur.

In 95% of cases, after about 3 weeks of uninhibited growth, the immune system suppresses bacillary replication. This may happen before symptoms or signs develop. Foci of infection in the lung or other sites resolve into epithelioid cell granulomas, which may have caseous and necrotic centres; tubercle bacilli can survive in this material for years, the host's resistance determining whether the infection ultimately resolves without treatment, remains dormant, or becomes active.

Foci may leave nodular scars in the apices of one or both lungs (Simon foci), calcified scars from the primary infection (Ghon foci), or calcified hilar lymph nodes. The tuberculin skin test is positive.
Rarely, the primary focus immediately progresses especially in infants or young children with other debilitating diseases, causing acute, potentially fatal, illness with pneumonia, pleural effusion, and marked mediastinal or hilar lymph node enlargement (which in children may compress bronchi). Small pleural effusions are predominantly lymphocytic, typically contain few organisms, and clear within a few weeks.

Primary extra-pulmonary TB at any site can sometimes present without evidence of lung involvement. While TB lymphadenopathy is the most common extra-pulmonary presentation, meningitis is the most feared because of its high mortality in the very young and very old.

**Active disease:**

In about 10% of patients overall, latent infection develops into active disease, although the percentage varies significantly depending on age and other risk factors. In 50 to 80% of those who develop active disease, TB reactivates within the first 2 years, but it can occur decades later. Any organ initially seeded may be a site of reactivation, but reactivation occurs most often in the lung apices, where O2 tension is highest.

Ghon foci and affected hilar lymph nodes are much less likely to be sites of reactivation.

Conditions that facilitate activation include:

- impaired immunity (particularly HIV infection)
- certain immunosuppressant drugs (eg, corticosteroids, infliximab and other tumour necrosis factor blockers (TNF antagonists)
- gastrectomy, jejunoileal bypass surgery, silicosis, renal insufficiency, stress, diabetes, head or neck cancer,
- Adolescence, and advanced age (> 70 yr).

TB damages tissues through delayed hypersensitivity, typically producing:

- Granulomatous necrosis with a caseous histological appearance.
- Cavitating Lung lesions
- Pleural effusions. This is less common than in progressive primary TB but may occur from direct extension or haematogenous spread.
- Rupture of a large tuberculous lesion into the pleural space may produce empyema with or without broncho-pleural fistula; it sometimes causes pneumothorax.

The course varies greatly, depending on the virulence of the organism and the state of host defences. The course may be rapid among African Americans, Afro-Caribbeans and American Indians who have not had as many centuries of selective pressure to develop innate or natural immunity.
Symptoms and Signs
In active pulmonary TB, even with moderate or severe disease, the patient may have no symptoms except ‘not feeling well’ or may have more specific symptoms.

Cough is most common.
At first, it may be minimally productive of yellow or green sputum, usually on rising, but cough may become more productive as the disease progresses.

Drenching night sweats are a classic symptom but are neither common in nor specific for TB.

Dyspnoea may result from lung parenchymal involvement, spontaneous pneumothorax, or pleural involvement with effusion.

Haemoptysis occurs only with cavitating TB.

Weight Loss

Recommended investigations

Latent TB
To diagnose latent TB:

- Mantoux testing should be performed
- Those with positive results (or in whom Mantoux testing may be less reliable) should then be considered for interferon-gamma immunological testing, if available.
- If testing is inconclusive, the person should be referred to a TB specialist.

Active TB
To diagnose active respiratory TB:

- a posterior–anterior chest X-ray should be taken; chest X-ray appearances suggestive of TB should lead to further diagnostic investigation
- multiple sputum samples (at least three, with one early morning sample) should be sent for TB microscopy and culture for suspected respiratory TB before starting treatment if possible or, failing that, within 7 days of starting
- spontaneously produced sputum should be obtained if possible. Otherwise induction of sputum (by inhalation of saline) or bronchoscopy and lavage should be used
Medical Services

- in children unable to expectorate sputum, induction of sputum should be considered if it can be done safely, with gastric washings considered as third line

If there are clinical signs and symptoms consistent with a diagnosis of TB, treatment should be started without waiting for culture results. The standard recommended regimen should be continued in patients whose subsequent culture results are negative.

Samples may be sent for TB culture from autopsy samples if respiratory TB is a possibility.

**Active non-respiratory TB:**
The advantages and disadvantages of both biopsy and needle aspiration should be discussed with the patient, with the aim of obtaining adequate material for diagnosis.

If non-respiratory TB is a possibility, part or all of any of the following samples should be placed in a dry pot (and not all placed in formalin) and sent for TB culture:

- lymph node biopsy
- pus aspirated from lymph nodes
- pleural biopsy
- any surgical sample sent for routine culture
- any radiological sample sent for routine culture
- histology sample
- aspiration sample (from pleural or pericardial effusions)
- autopsy sample

TB culture should routinely be performed on the above samples.
The appropriate treatment regimen should be started without waiting for culture results if the histology and clinical picture are consistent with a diagnosis of TB.

All patients with non-respiratory TB should have a chest X-ray to exclude or confirm co-existing respiratory TB.
The appropriate drug regimen should be continued even if subsequent culture results are negative.
Table 1 Suggested site-specific investigations in the diagnosis and assessment of non-respiratory TB

<table>
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<th>Site</th>
<th>Imaging</th>
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| Bone/joint            | • Plain X-ray and computed tomography (CT)  
                       |                               | • Site of disease                   | • Biopsy or paraspinal abscess         
                       | • Magnetic resonance imaging (MRI)       |                               | • Site or joint fluid                 |
| Gastrointestinal      | • Ultrasound                       | • Omentum                    | • Biopsy                                 |
                       | • CT abdomen                      | • Bowel                      | • Ascites                                 |
| Genitourinary         | • Intravenous urography            | • Site of disease            | • Early morning urine (x3)                 |
                       | • Ultrasound                      |                               | • Site of disease                        |
                       |                                 |                               | • Endometrial curettings                |
| Disseminated          | • High-resolution CT thorax         | • Lung                       | • Bronchial wash                          |
                       | • Ultrasound abdomen              | • Liver                      | • Liver                                  |
                       |                                 | • Bone marrow                | • Bone marrow                            |
| Central nervous system| • CT brain                        | • Tuberculoma                | • Blood                                  |
                       | • MRI                            |                               |                                           |
| Skin                  |                                 | • Site of disease            | • Site of disease                         |
| Pericardium           | • Echocardiogram                  | • Pericardium                | • Pericardial fluid                      |
| Cold/liver abscess    | • Ultrasound                      | • Site of disease            | • Site of disease                         |
Medical Services

Treatment

Management of respiratory TB

Respiratory TB is defined as active TB that is affecting any of the following:
- lungs
- pleural cavity
- mediastinal lymph nodes
- larynx

Drug treatment

Once a diagnosis of active TB is made, the clinician responsible for care should refer the person with TB to a physician with training in, and experience of, the specialised care of people with TB.

TB in children should be managed either by a paediatrician with experience and training in the treatment of TB, or by a general paediatrician with advice from a specialised physician.

A 6-month, four-drug initial regimen (6 months of Isoniazid and Rifampicin supplemented in the first 2 months with Pyrazinamide and Ethambutol) should be used to treat active respiratory TB in:
- adults not known to be HIV-positive
- adults who are HIV-positive
- children

This regimen is referred to as ‘standard recommended regimen’.

Fixed-dose combination tablets should be used as part of any TB treatment regimen.

Cure is possible in Multi-drug Resistant T B (MDRTB) using prolonged treatment with less effective, more expensive and more toxic drugs. However, further resistance may develop and there is a high risk of treatment failure.

Infection control

All patients with TB should have risk assessments for drug resistance and for HIV.

A significant proportion of patients with TB do not require to be admitted to hospital. Others require admission because they are seriously ill or require inpatient investigations. In addition admission may be indicated for socio-economic reasons perhaps where there are doubts about drug compliance due to learning difficulties or severe mental health problems including addictions.

If admitted to hospital, patients with suspected respiratory TB should be given a single room.

Patients with respiratory TB should be separated from immuno-compromised patients, either by admission to a single room on a separate ward, or to a negative-pressure room on the same ward.
Any visitors to a child with TB in hospital should be screened as part of contact tracing, and kept separate from other patients until they have been excluded as the source of infection.

Smear-positive TB patients without risk factors for Multi-Drug Resistant TB (MDR TB) should be cared for in a single room, until:
- they have completed 2 weeks of the standard recommended regimen, or
- they are discharged from hospital

Aerosol-generating procedures such as bronchoscopy, sputum induction or nebuliser treatment should be carried out in an appropriately engineered and ventilated area for:
- all patients on an HIV ward, regardless of whether a diagnosis of TB has been considered
- all patients in whom TB is considered a possible diagnosis, in any setting

Healthcare workers caring for people with TB should not use masks, gowns or barrier nursing techniques unless:
- MDR TB is suspected
- aerosol-generating procedures are being performed
  When such equipment is used, the reason should be explained to the person with TB.

The equipment should meet the standards of the Health and Safety Executive.

TB patients admitted to a setting where care is provided for HIV-positive or other immunocompromised patients should be considered infectious and should stay in a negative-pressure room until:

(a) For people who were sputum smear positive at admission:
1. they have had had at least 2 weeks of appropriate multiple drug therapy, and
2. if moving to accommodation (inpatient or home) with HIV-positive or immunocompromised patients, have had at least three negative microscopic smears on separate occasions over a 14-day period, and
3. are showing tolerance to the prescribed treatment and an ability and agreement to adhere to treatment, and either
4. any cough has resolved completely, or
5. there is definite clinical improvement on treatment, for example remaining afebrile for a week

(b) For people who were sputum smear negative at admission (that is, three negative samples were taken on separate days; samples were spontaneously produced sputum if possible, or obtained by bronchoscopy or lavage if sputum samples were not possible):
all of 1, 2, 3 and 5 above should apply.

Inpatients with smear-positive respiratory TB should be asked (with explanation) to wear a surgical mask whenever they leave their room until they have had 2 weeks of drug treatment.

Management of non-respiratory TB - See Appendix A
Prognosis

In immuno-competent patients with drug-susceptible pulmonary TB, even severe disease and large cavities usually heal if appropriate therapy is instituted and completed.

TB still causes or contributes to death in about 10% of cases, often in those who are debilitated for other reasons.

Disseminated TB and TB meningitis may be fatal in up to 25% of cases despite optimal treatment. TB is much more aggressive in immuno-compromised patients and, if not properly and aggressively treated, may be fatal in as little as 2 months from its initial symptom. This is especially true of Multi-Drug Resistant TB (MDR- TB), in which mortality can approach 90%.
Main Disabling Effects

Severe disability is uncommon unless the claimant has been ineffectively treated or is immunocompromised but can arise e.g. following TB affecting the CNS, pericardium or urogenital tracts.

Respiratory TB
Even in active pulmonary TB with moderate disease, the patient may have few symptoms and only very minimal disability due to a general malaise. Occasionally there may be a cough and/or night sweats which affect sleep and so add to the general malaise.

Dyspnoea may result from lung parenchymal involvement and in this situation disability is unlikely to be more than mild to moderate.

Spontaneous pneumothorax may give rise to an acute episode of breathlessness but should resolve with the appropriate treatment.

Pleural involvement with effusion is likely to produce the longest period of breathlessness while any significant effusion is present.

Pulmonary TB would normally be expected to respond to the anti-tuberculous medication with progressive reduction and complete resolution of symptoms over a period of 3 months.

Non-respiratory TB

Lymph Nodes
Affected nodes are swollen and may be mildly tender or drain. Adjacent nodes sometimes coalesce into an irregular mass. Usually the hilar lymph nodes are involved. Other nodes generally are not involved unless disease is poorly contained, allowing organisms to reach the thoracic duct, where they disseminate into the bloodstream. Most infected nodes heal, but reactivation commonly occurs. Infection in supraclavicular nodes may inoculate anterior cervical nodes, eventually resulting in Scrofula - TB lymphadenitis in the neck.

TB peritonitis:
Symptoms may be mild, with fatigue, abdominal pain, and tenderness, or severe enough to mimic acute abdomen.

The “doughy abdomen” referred to in old textbooks is rarely present.

TB pericarditis:
Pericardial infection may develop from foci in mediastinal lymph nodes or from pleural TB. In some high incidence parts of the world, TB pericarditis is a common cause of heart failure.

In Africa TB pericarditis is a common feature of AIDS. Constrictive pericarditis or tamponade may occur, producing dyspnoea, neck vein distension, paradoxical pulse, muffled heart sounds, and possibly hypotension.
TB of bones and joints
Symptoms include progressive or constant pain in involved bones and chronic or subacute arthritis (usually monoarticular). In Pott's disease, spinal cord compression produces neurological deficits, including paraplegia; paravertebral swelling may result from an abscess. Weight-bearing joints are most commonly involved, but bones of the wrist, hand, and elbow also may be affected, especially after injury.

Gastrointestinal TB:
Gastrointestinal TB is usually caused by swallowing infected sputum. Intestinal invasion generally produces hyperplasia and an inflammatory bowel syndrome with pain, diarrhoea, obstruction, and melaena. It may also mimic appendicitis. Ulceration and fistulae are possible.

TB of the liver:
Liver infection is common with advanced pulmonary TB and widely disseminated or miliary TB. However, the liver generally heals without sequelae when the principal infection is treated. TB in the liver occasionally spreads to the gallbladder, leading to obstructive jaundice.

TB meningitis:
Meningitis often occurs in the absence of infection at other extra-pulmonary sites. At any age, meningitis is the most serious form of TB and has high morbidity and mortality. It is the one form of TB believed to be prevented in childhood by vaccination with BCG.

Symptoms are low-grade fever, unremitting headache, nausea, and drowsiness, which may progress to stupor and coma.

Kernig's and Brudzinski's signs may be positive.
Stages are:
- clear sensorium with abnormal CSF,
- drowsiness or stupor with focal neurological signs, and
- Coma.

Stroke may develop due to thrombosis of a major cerebral vessel. Focal neurological symptoms suggest a tuberculous mass intracranial lesion (tuberculoma).

Genitourinary TB:
Infection of the kidney may present as pyelonephritis (e.g. fever, back pain, pyuria) without the usual urinary pathogens on routine culture ("sterile pyuria"). Infection commonly spreads to the bladder and, in men, to the prostate, seminal vesicles, or epididymis, causing an enlarging scrotal mass. Infection may spread to the perinephric space and down the psoas muscle, sometimes causing an abscess on the anterior thigh.

In women, salpingo-oophoritis can occur after menarche, when the fallopian tubes become vascular. Symptoms include chronic pelvic pain and sterility or ectopic pregnancy from tubal scarring.
Miliary TB:
Also known as generalized haematogenous TB, miliary TB occurs when a tuberculous lesion erodes into a blood vessel, disseminating millions of tubercle bacilli into the bloodstream and throughout the body. The lungs and bone marrow are most often affected, but any site may be involved.

Miliary TB is most common in children under 4 years old, immuno-compromised people, and the elderly.

Symptoms include fever, chills, weakness, malaise, and often progressive dyspnoea. Intermittent dissemination of tubercle bacilli may lead to a prolonged PUO (Pyrexia of Unknown Origin). Bone marrow involvement may produce anaemia, thrombocytopenia, or a leukaemoid reaction.

Other sites:
Rarely, TB may develop on abraded skin in a patient with cavitating pulmonary TB. TB may infect the wall of a blood vessel and has even ruptured the aorta. Adrenal involvement, leading to Addison's disease, formerly was common but now is rare. Trauma to a tendon sheath may cause tuberculous tenosynovitis in a patient with tuberculous involvement of any organ.
B. SARCOIDOSIS
Introduction

Definition

*Sarcoidosis is characterized by non-caseating granulomas in one or more organs and tissues and is of unknown aetiology.*

The lungs and lymphatic system are most often affected, but sarcoidosis may affect any organ.

Diagnosis usually is first suspected because of pulmonary involvement and is confirmed by chest x-ray, biopsy, and exclusion of other causes of granulomatous inflammation.

First-line treatment is corticosteroids.

Prognosis is excellent for limited disease but poor for more advanced disease.
Description

Epidemiology

Sarcoidosis primarily affects people aged 20 to 40 but occasionally affects children and older adults.

Prevalence

Worldwide, prevalence is greatest in black Americans and northern Europeans, especially Scandinavians, who have one of the highest incidence rates at 64 cases per 100,000 population. This contrasts with Poland, where the incidence is reported as 3 cases per 100,000 population.

The disease is rare in Eskimos, Southeast Asians, New Zealand Maoris, and native Canadian populations.

Disease presentation varies widely by racial and ethnic background, with black Americans and Puerto Ricans demonstrating more frequent extra thoracic manifestations.

Sarcoidosis is slightly more prevalent in women.

Incidence increases in winter and early spring, for unknown reasons. Although sarcoidosis can appear at any age, a bimodal age distribution is seen, which peaks between ages 25-35 and 45-65 years.

Aetiology

The cause of sarcoidosis remains obscure. One hypothesis is that sarcoidosis is an inflammatory response to an environmental agent (including infectious) which occurs in a susceptible host. Susceptibility is influenced by genetic predisposition.

Several potential infectious agents have been proposed as causes of sarcoidosis. Although non-caseating, the granulomatous reaction reminds many of tuberculosis, and much effort has been expended trying to identify a mycobacterial cause. Several studies using polymerase chain reaction (PCR) and similar molecular biological techniques have been employed, but there is still no convincing evidence that Mycobacterium tuberculosis causes most cases of sarcoidosis. It may lead to an occasional case of sarcoid-like reaction. Other mycobacteria have been identified in some cases. Cell wall-deficient mycobacteria have been grown from the blood of patients with sarcoidosis. However, a recently completed control trial failed to demonstrate a difference in the incidence of cell wall-deficient mycobacteria between those with sarcoidosis and controls.
Pathophysiology

Sarcoidosis is defined by its immunological reaction, the granuloma. Original immunological studies stressed a lack of systemic immune response by the patient with sarcoidosis. This includes anergy, the lack of reaction to any skin test, which is a common feature of active sarcoidosis. A reduction in circulating leucocytes, especially lymphocytes, is an important feature of the disease.

In the 1970s, new techniques helped in the understanding of sarcoidosis. The most important tool introduced at the time was bronchoalveolar lavage, which provided a sample of the inflammatory cells in the lower respiratory tract. In normal lavage fluid, alveolar macrophages are the usual resident inflammatory cell retrieved; lymphocytes and neutrophils are found much less frequently. In lavage fluid from patients with active sarcoidosis, the preponderance of T lymphocytes is usually increased. These lymphocytes are often T-helper/inducer cells (CD4+), and the ratio of CD4 to CD8 lymphocytes is increased from that normally found in the blood (0.8 to 2.2), often to greater than 3.5.

The CD4 lymphocyte is a crucial cell in cell-mediated immunity. The CD4 lymphocytes are activated and release several cytokines, including interleukin 2 (IL-2) and γ-interferon. The T lymphocyte can mount either a TH1 or TH2 response. The TH1 response is associated with granuloma formation, while TH2 is associated with an eosinophilic response and fibrosis. The initial response of sarcoidosis follows a TH1 pattern. The lymphocytes release IL-2 spontaneously, and γ-interferon is released by both lymphocytes and macrophages. An increase in IL-12 and lower levels of IL-10 have also recently been described, consistent with a TH1 response.

The resolution of sarcoidosis has also been studied with serial lavages. The T lymphocytes remain elevated for some time, but the proportion of CD4 to CD8 decreases to the normal ratio found in blood (0.8 to 2.2). The amount of cytokines released also decreases. This return to normal of the inflammatory response has been shown to occur during treatment of sarcoidosis with corticosteroids or methotrexate.

Genetic factors

Familial clustering of cases has been reported. Monozygotic twins are 2-4 times as likely to have the disease as dizygotic twins.

Certain HLA associations have been demonstrated; the most common allele found in sarcoidosis is HLA-B8. Other associated alleles include HLA-A1 and HLA-DR3.

Affected organs

Commonly affected organs include the lung, skin, and eyes. Less commonly, the liver, heart, and brain are affected by the disease. Individual organ involvement by sarcoidosis can be proved by a biopsy showing non-caseating granuloma.

Presumed organ involvement is assumed if certain criteria are met. Table 2 lists some of the criteria suggested for definite or probable organ involvement for some of the more commonly affected organs in sarcoidosis.
Medical Services

Lung
Radiological evidence of respiratory involvement has been described in more than 90 per cent of patients. The lung involvement includes both the lymph nodes and the lung parenchyma.

Scadding and Wurm independently described four stages of the chest radiograph:
- stage 1 is hilar adenopathy alone,
- stage 2 is adenopathy and parenchymal disease,
- stage 3 is parenchymal disease alone, and
- stage 4 is fibrosis

Fibrotic changes due to sarcoidosis are usually in the upper lobe, with retraction.

The staging system has proved useful in standardizing reports of pulmonary level of involvement. It has also proved a useful prognostic measure. Patients with stage 1 disease have a 90 per cent rate of resolution within 2 to 3 years, while patients with stage 3 disease possess only a 30 per cent chance of resolution.

However, it does not predict the degree of extra-pulmonary disease. The choice of the term ‘stage’ is therefore unfortunate. However, it is so standard that it will not be easily replaced.

The use of the CT scan has changed our evaluation of many interstitial lung diseases.

In sarcoidosis, peribronchial thickening is often seen in the upper lobe. Adenopathy is usually seen in sarcoidosis, making the staging system only applicable for plain radiographs. The CT scan may identify adenopathy in a patient with possible extra-pulmonary sarcoidosis. This may help in deciding where to proceed with a tissue diagnosis (lung biopsy or mediastinoscopy). Pulmonary function studies in patients with sarcoidosis classically demonstrate a restrictive pattern, with reduction of lung volumes. The transfer factor is usually reduced out of proportion to the loss of lung volume, as one would expect in an interstitial lung disease.

In advanced cases, the oxygen level will be reduced, especially during exercise.

Obstructive disease can also occur in sarcoidosis. This can be due to airway involvement by the sarcoidosis or associated with cough, a common complaint in the condition.

Skin
The skin is the second most commonly affected organ in sarcoidosis. There are six major manifestations.

Hyperpigmentation, hypopigmentation, and keloid reaction may demonstrate granulomas on biopsy. However, their appearance is not always specific. Waxy, maculopapular lesions, which occur on the extremities, back, and face, are usually raised, with the majority less than 2 cm in diameter.
When these occur on the face, especially on the cheeks and nose, they are called lupus pernio.

Erythema nodosum (red nodular lesions on the extremities which are acutely tender) usually involves the legs. The constellation of erythema nodosum, arthritis (in the ankles), hilar adenopathy, and uveitis is referred to as Lofgren’s syndrome and is a diagnostic manifestation of sarcoidosis. It is associated with a good prognosis. Interestingly, the skin lesions from erythema nodosum do not contain granulomas, but are considered to be due to circulating immune complexes from the disease.

**Eye**
The eye can be affected in more than 20 per cent of patients with sarcoidosis. The most common findings are uveitis and lacrimal gland involvement. Anterior uveitis is often self-limiting, and can be treated topically; however, posterior uveitis is a more chronic form of the disease and may require injections of corticosteroids or systemic therapy.

Sicca (dry eyes) and glaucoma are long-term complications which are encountered in patients often years after other sarcoidosis symptoms have resolved. They are consequences of the fibrotic changes in the lacrimal glands and eye. They do not respond to anti-inflammatory therapy.

Optic nerve involvement can be seen with sarcoidosis, with idiopathic disease and multiple sclerosis being the other major causes of this sight-threatening complication.

Retinal disease has also been reported. Fortunately, blindness from sarcoidosis is rare, and usually a consequence of untreated uveitis, retinitis, or optic neuritis.

**Neurological**
Neurological disease from sarcoidosis includes cranial nerve, central nervous system, and peripheral nerve involvement.

Bell’s palsy (seventh cranial nerve) is a common complaint in neurosarcoidosis. Central nervous system lesions can lead to a lymphocytic meningitis. Hypothalamic involvement is a characteristic finding, with diabetes insipidus as a resulting complaint.

The use of contrast-enhanced magnetic resonance imaging is the most sensitive method for detecting central nervous system disease. The lumbar puncture is complementary, with increased protein and lymphocytes often seen in active disease. Detection of angiotensin-converting enzyme in the spinal fluid is suggestive but not diagnostic of neurosarcoidosis.

**Other manifestations**
Liver and spleen involvement may be found in over half of patients with sarcoidosis. However, symptomatic disease occurs in less than 10 per cent of patients. Often, elevated liver function tests (especially the alkaline phosphatase and γ-glutamyl transferase) are seen, suggesting an obstructive pattern. Hyperbilirubinaemia is relatively rare, but implies extensive disease and is usually an indication for therapy. Massive splenomegaly can occur, and occasionally splenectomy is performed to avoid rupture.
Hypercalcaemia and hypercalcinuria are seen with sarcoidosis. The mechanism is related to the effect of the granuloma on vitamin D3. The granuloma itself converts the vitamin D3 to the biologically active form 1,25-D3. This form of the vitamin has immunological activity as well as enhancing calcium absorption from the gastrointestinal tract. In some patients with sarcoidosis, the 1,25-D3 can leak into the bloodstream and produce a systemic effect. Increased sunlight exposure also increases the levels of 1,25-D3.

In America, hypercalcaemia is far more common in Caucasian than African-American individuals. Because of the effect of increased calcium absorption, urolithiasis may also be seen in patients with sarcoidosis. Recently, it has been recognised to be a marker for chronic disease.

A less common, but serious complication of sarcoidosis is cardiac involvement. Direct involvement of the heart can lead to arrhythmias such as heart block and ventricular ectopy. This can lead to sudden death. If the problem is recognized, the use of an implanted defibrillator may reduce this risk.

Cardiomyopathy is also seen, and cardiac sarcoidosis should be considered in a young patient who presents with unexpected heart failure. Endomyocardial biopsy rarely makes a diagnosis, since the granulomas are patchy. The technetium scan showing non-segmental fixed defects is the most sensitive. Gallium uptake of the heart is more specific than a thallium scan.

Sarcoidosis granulomas can involve virtually any organ of the body. Rare manifestations include bone cysts, usually in the distal portion of the fingers, sinus invasion, pleural disease, breast disease, and ovarian or testicular masses.

The multi-organ involvement of sarcoidosis distinguishes it from other diseases. Lymphoma and tuberculosis are two diseases often considered in the differential diagnosis of patients with possible sarcoidosis.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Suggestive features</th>
<th>Possible features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Positive biopsy of lung</td>
<td>Lymphocytic alveolitis by bronchoalveolar lavage</td>
</tr>
<tr>
<td></td>
<td>Chest radiograph characteristic for sarcoidosis (hilar adenopathy, diffuse infiltrates, or upper lobe fibrosis)</td>
<td>Any other pulmonary infiltrate</td>
</tr>
<tr>
<td></td>
<td>Pulmonary function tests showing restriction</td>
<td>Isolated reduction of DLCO</td>
</tr>
<tr>
<td>Skin</td>
<td>Positive biopsy of skin</td>
<td>Macular/papular lesion</td>
</tr>
<tr>
<td></td>
<td>Lupus pernio</td>
<td>New nodules (including subcutaneous)</td>
</tr>
<tr>
<td></td>
<td>Erythema nodosum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annular lesion</td>
<td></td>
</tr>
<tr>
<td>Organ</td>
<td>Suggestive features</td>
<td>Possible features</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Neurological (con’d)</td>
<td>Diabetes insipidus</td>
<td>Cardiomyopathy or ventricular arrhythmias without other cardiac problems</td>
</tr>
<tr>
<td></td>
<td>Cranial seventh nerve paralysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other cranial nerve dysfunction</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>Positive cardiac biopsy</td>
<td>Positive thallium scan</td>
</tr>
<tr>
<td></td>
<td>Treatment-responsive cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECG showing intraventricular or nodal block</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive gallium scan of heart</td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis

Symptoms and Signs

Patients with sarcoidosis may have a variety of presentations.

**Lung Symptoms**
- Shortness of breath
- An unproductive cough
- Wheezing
- Pain in the middle of the chest that gets worse when breathing deeply or coughing (rare).

**Lymph Node Symptoms**
- Enlarged and sometimes tender lymph nodes—most often those in the neck and chest but sometimes those under the chin, arm pits, or in the groin.

**Skin Symptoms**
- Various types of bumps, ulcers, or, rarely, flat areas of discoloured skin, that appear mostly near the nose, eyes, back, arms, legs, and scalp. They usually itch but aren't painful. They may last a long time.
- Painful bumps that usually appear on the ankles and shins and can be warm, tender, red or purple-to-red in colour, and slightly raised (erythema nodosum). These bumps may be associated with fever and swollen ankles and joint pain.
- Disfiguring skin sores that may affect the nose, nasal passages, cheeks, ears, eyelids, and fingers (lupus pernio). The sores tend to be ongoing and can return after treatment is over.

**Eye Symptoms**
- Burning, itching, tearing, pain
- Red eye
- Sensitivity to light
- Dryness
- Floaters (i.e., seeing black spots)
- Blurred vision
- Reduced colour vision
- Reduced visual acuity
- Blindness (in rare cases).

**Heart Symptoms**
- Shortness of breath
- Swelling in the legs
- Wheezing
- Coughing
- Irregular heartbeat,
- Sudden loss of consciousness
- Sudden death.
Joint and Muscle Symptoms
- Joint stiffness or swelling—usually in the ankles, feet, and hands.
- Joint pain.
- Myalgia.
- Muscle pain, a mass in a muscle, or muscle weakness.
- Painless arthritis that can last for months or even years. It should be treated.

Bone Symptoms
- Painless holes in the bones.
- Painless swelling, most often in the fingers.
- Anaemia from granulomas affecting the bone marrow. This usually requires treatment.

Liver Symptoms
- Fatigue
- Itching
- Pain in the upper right quadrant of the abdomen, under the right ribs
- Enlarged liver.

Parotid and Other Salivary Gland Symptoms
- Swelling
- Excessive dryness in the mouth and throat.

Blood, Urinary Tract, and Kidney Symptoms
- Increased calcium in the blood or urine, which can lead to kidney stones
- Confusion
- Polyuria which may be due to hypercalcaemia/renal impairment or diabetes insipidus

Nervous System Symptoms
- Headaches.
- Vision problems.
- Weakness or numbness of an arm or leg.
- Coma (rare).
- 7th nerve palsy. This can be confused with Bell's palsy, a disorder that may be caused by a virus.
- Paralysis of the arms or legs, from spinal cord involvement.
- Weakness, pain, or paraesthesia in areas where many nerves are affected.

Pituitary Gland Symptoms (Rare)
- Headaches
- Vision problems
- Weakness or numbness of an arm or leg
- Coma (rare).

Other Symptoms
- Nasal obstruction or frequent bouts of sinusitis.
- Enlarged spleen, which leads to a decrease in platelets in the blood and splenic pain.
Sarcoidosis may also cause more general symptoms, including:

- Uneasiness, feeling sick (malaise), an overall feeling of ill health
- Tiredness, fatigue, weakness
- Loss of appetite or weight
- Fever
- Night sweats
- Sleep problems

(All these general symptoms are often caused by other conditions.)

### Differential Diagnosis of Sarcoidosis

#### Infectious

- **Bacterial**
  - Mycobacterial
  - TB
  - Atypical mycobacteria
  - Syphilis

- **Fungal**
  - Aspergillosis
  - Blastomycosis
  - Coccidioidomycosis
  - Cryptococcal infection
  - Histoplasmosis

- **Other**
  - Brucellosis
  - Cat-scratch disease (lymph nodes only)
  - Mycoplasmal infection
  - Pneumocystis jiroveci (formerly P. carinii)

#### Rheumatological

- Juvenile RA
- Kikuchi’s lymphadenitis (lymph nodes only)
- Sjögren’s syndrome
- Wegener’s granulomatosis

#### Haematological malignancy

- Hodgkin lymphoma
- Non-Hodgkin lymphoma
- Splenic lymphoma

#### Hypersensitivity

- **Occupational metals**
  - Aluminium, Berylliosis
  - Titanium
  - Zirconium

- **Organic antigens producing hypersensitivity pneumonitis**
  - Actinomycetes
  - Atypical mycobacterial antigens
  - Fungi Mushroom spores
  - Other bio aerosols
Inorganic antigens producing hypersensitivity pneumonitis
- Isocyanates
- Pyrethrins
- Drug reaction

Other
- Inflammatory bowel disease
- Foreign body aspiration or inoculation
- Granulomatous hepatitis
- Granulomatous lesion of unknown significance
- Lymphoid interstitial pneumonia

Investigations

Because the cause of sarcoidosis is unknown, one can never be absolutely confident of the diagnosis, which is always one of exclusion. However, the finding of non-caseating granulomas in two or more organs is considered diagnostic. Cultures and special stains for tuberculosis and deep-seated fungal infections should be taken to rule out infection as the cause of granulomas. Close examination should also be made for foreign bodies and malignancy, both of which can lead to a granulomatous reaction.

Serum angiotensin-converting enzyme (ACE) levels
In 1976, Lieberman reported that ACE level was elevated in the blood of some patients with sarcoidosis.

Determining the significance of the ACE level in sarcoidosis can be difficult for a variety of reasons.

Sixty per cent of patients with acute disease will have elevated values, whilst only 10 per cent of patients with disease for more than 2 years will continue to have an elevated level.

The ACE level will decrease in response to treatment or disease resolution, and it has therefore been proposed as a marker for disease activity.

Tests of the lung
**Bronchoalveolar lavage**: findings can be characteristic in sarcoidosis. The finding of increased lymphocytes, especially an increased CD4 to CD8 ratio, has been interpreted by some groups as enough to make the diagnosis of sarcoidosis, and in a patient with a compatible clinical history and no evidence for infection or malignancy, the lavage findings may be considered sufficient.

**Bronchoscopy**: includes a transbronchial biopsy showing non-caseating granulomas. In over 60 per cent of patients with a stage 1 chest radiograph the biopsy should be positive, rising to 80 per cent in patients with stage 2 or 3 disease.
Transbronchial needle aspiration: has recently been used to sample hilar lymph nodes, but raises the problem of incomplete sampling in patients with a malignancy and granulomatous response to the lesion.

Mediastinoscopy and video-assisted thoracoscopy provide a minimally invasive method to obtain more tissue.

Gallium scan can reveal increased activity in patients with sarcoidosis. Unfortunately, interpreting the uptake in the lung may be difficult as it is non-specific and occurs with other inflammatory lung diseases. It also rapidly returns to normal with corticosteroid therapy. On the other hand, the uptake in the parotid and conjunctiva (the ‘panda’ sign) and the uptake in the hilar nodes (the ‘lambda’ sign) are fairly characteristic for sarcoidosis and are useful confirmation in difficult cases.

Other tests
The Kveim–Siltzbach agent is a suspension of spleen tissue from a patient with confirmed sarcoidosis. Six weeks after an intradermal injection of the agent, the site is inspected for a reaction, which will occur in over 60 per cent of patients with acute sarcoidosis. On biopsy, the reaction will show non-caseating granulomas, consistent with sarcoidosis. Properly prepared Kveim–Siltzbach agent has a less than 1 in 500 chance of causing a false positive. However, because of the difficulties in preparing the agent and concerns regarding the risk of transmission of an infectious agent, the test is rarely used except in those centres with a well established reagent.
Management

The natural course of sarcoidosis is unclear, since corticosteroids are normally used to treat symptomatic patients. For the patient with no symptoms on presentation, the prognosis is often good and no treatment is indicated. This also applies to patients in whom spontaneous resolution can be anticipated. Spontaneous resolution commonly occurs within a year or two of diagnosis, but the disease can also take a chronic form, with symptoms for many years. The concept of acute disease, which lasts for less than 2 years, as opposed to chronic disease has been a useful method for considering patients, especially in terms of therapy. The table below lists several factors associated with resolution within 2 to 5 years as well as those predicting chronic disease.

Table 3

<table>
<thead>
<tr>
<th>Organ</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiograph</td>
<td>Stage 1</td>
<td>Stage 4</td>
</tr>
<tr>
<td>Skin</td>
<td>Erythema nodosum</td>
<td>Lupus pernio</td>
</tr>
<tr>
<td>Eyes</td>
<td>Anterior uveitis</td>
<td>Posterior uveitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pars planitis</td>
</tr>
<tr>
<td>Joint involvement</td>
<td></td>
<td>Bone cysts</td>
</tr>
<tr>
<td>Calcium metabolism</td>
<td>Hypercalcaemia</td>
<td>Renal stones</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Neurological</td>
<td>Cranial seventh nerve palsy</td>
<td>Central nervous system mass</td>
</tr>
<tr>
<td>Sinus</td>
<td></td>
<td>Sinus involvement</td>
</tr>
</tbody>
</table>

The major indication for therapy in sarcoidosis is symptoms.

Hypercalcaemia should be treated, even if the patient is asymptomatic.

An eye examination should be performed in all patients with sarcoidosis. Uveitis may be misdiagnosed as sicca (dry eyes). The former will require anti-inflammatory agents, while the latter will only need a wetting agent. If possible, treatment should be topical. Corticosteroid creams and eye drops are effective if inflammation is superficial.

It is not clear whether corticosteroids change the natural course of the disease. Early randomized trials found no difference in the long-term outcome of patients who received corticosteroids compared with controls. A British Thoracic Society randomized study did demonstrate a small benefit for corticosteroids over placebo for patients with persistent, but not severe, disease. One of the difficulties in assessing this and other trials is that the more severely affected patients were treated with corticosteroids and excluded from the study.
Once systemic steroids are initiated a prolonged course is usually necessary.

In the beginning, doses may be changed every 1 to 3 months, but after a patient remains stable on a lower dose (equivalent to less than 10 mg of prednisolone per day), tapering may be prolonged. The use of alternate-day corticosteroids is strongly advocated by some, but others are less enthusiastic. Rarely will alternate-day therapy be sufficient for initial control of the disease.

The toxicity of corticosteroids is well known. Unfortunately, most patients will require more than a year of treatment.

Several alternatives to systemic corticosteroids have been proposed over the years.

Table 4

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Efficacy (%)</th>
<th>Toxicity</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone/prednisolone</td>
<td>5–40 mg/day</td>
<td>90</td>
<td>Weight gain, diabetes, hypertension, osteoporosis, psychiatric</td>
<td>Acute, chronic, refractory</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10–25 mg once a week</td>
<td>60–80</td>
<td>Haematological, gastrointestinal, lung, hepatic, mutagenic</td>
<td>Chronic, refractory</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>200–400 mg/day</td>
<td>30–50</td>
<td>Gastrointestinal, retinal</td>
<td>Acute, chronic</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>50–200 mg/day</td>
<td>50–80</td>
<td>Haematological, gastrointestinal, carcinogenic, mutagenic</td>
<td>Chronic</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>400 mg three times a day</td>
<td>50</td>
<td>Gastrointestinal</td>
<td>Acute</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>50–150 mg/day orally,</td>
<td>80</td>
<td>Gastrointestinal, haematological,</td>
<td>Chronic, refractory</td>
</tr>
<tr>
<td></td>
<td>500–2000 mg every 2 weeks intravenously</td>
<td></td>
<td>carcinogenic, bladder, teratogenic</td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>50–100 mg/day</td>
<td>80</td>
<td>Teratogenic, somnolence, peripheral neuropathy</td>
<td>Chronic, refractory</td>
</tr>
</tbody>
</table>

The commonly prescribed antimalarial agents chloroquine and hydroxychloroquine possess anti-inflammatory activity with their major toxicities being eye and gastrointestinal. Because hydroxychloroquine, especially at 400 mg a day or less, is unlikely to cause eye toxicity, it is more frequently prescribed. However, some experts feel chloroquine is a more effective agent. These drugs concentrate in the skin and are most efficacious for skin disease and hypercalcaemia. They are less successful in the treatment of pulmonary disease.
In sarcoidosis, **methotrexate** has been most studied as a treatment for chronic disease. This probably reflects the fact that it may require 6 months for the drug to become effective. The usual dose is 10 to 15 mg orally each week, adjusted if this proves toxic. Acute toxicity including mucositis and nausea can be minimized with supplements of folic acid at 1 mg/day. The long-term toxicity of methotrexate can include hypersensitivity pneumonitis and cirrhosis. The latter is a concern, because 50 per cent of patients with chronic disease will have sarcoid granulomas in a liver biopsy, and thus liver biopsies are recommended every 2 years for patients requiring the drug long term.

The response rate to methotrexate in chronic sarcoidosis is 60 to 80 per cent. Most patients who respond can be treated with methotrexate alone. Approximately 20 per cent of patients will require additional low-dose corticosteroids. In most patients skin lesions can be easily controlled with methotrexate, but studies have also reported benefit for disease in the lungs, eyes, and nervous system.

**Azathioprine** has been used for many years as an immunosuppressant for patients receiving solid-organ transplants and those with idiopathic pulmonary fibrosis. However, its use in sarcoidosis has been more sporadic, usually reserved for chronic cases. Its major side-effects are gastrointestinal and haematological.

Other drugs have been used for refractory sarcoidosis.

- **Cyclophosphamide** is used in the treatment of many vasculitic diseases and has been reported as very useful in neurological and cardiac sarcoidosis, but it has more gastrointestinal, haematological, and bladder toxicity than methotrexate or azathioprine.

- **Cyclosporin** has been used with limited success in some neurological cases. A recent randomized trial failed to show additional benefit over corticosteroids alone in patients with pulmonary sarcoidosis. The drug is relatively expensive, causes hypertension and renal failure, and requires blood levels to be monitored.

- **Pentoxyfylline** has been shown by one centre to provide some benefit in acute sarcoidosis. It is associated with significant gastrointestinal toxicity, which is dose dependent.

**There is no single treatment for all patients with sarcoidosis.**

It is important to determine whether the patient requires treatment. The decision to treat is usually based on the patient’s symptoms.

The clinician needs to determine the extent of the symptomatic disease and whether the disease is acute or chronic. Asymptomatic or minimally symptomatic patients with hypercalcaemia, cardiac, or central nervous system disease may require therapy to prevent life-threatening complications.
The use of systemic therapy usually means corticosteroids first. However, over time, the patient and the physician may need to seek alternatives.
Prognosis

The course of sarcoidosis is variable, ranging from self-limiting acute disease to a chronic debilitating disease that may result in death.

the majority of cases will resolve within 2 to 5 years

Approximately 25 per cent of patients will develop residual fibrosis

10-30% of patients have a more chronic or progressive course. For the patient with chronic disease, treatment can usually palliate the symptoms. However, organ failure, including eye, liver, cardiac, or respiratory, can occur as a result of disease.

The mortality rate is 1-6%. Sarcoidosis can lead to death from severe involvement of lung parenchyma leading to pulmonary fibrosis and respiratory failure and from myocardial involvement leading to arrhythmias and cardiac failure

Organ transplantation has been performed successfully in patients with sarcoidosis. Although sarcoidosis lesions can occur in the new organ, organ failure due to recurrent sarcoidosis is unlikely.
Main Disabling Effects

Respiratory disease

As 90% of cases involve the lungs the common disabilities arising from sarcoidosis are due to impaired lung function.

- Shortness of breath
- A dry cough that doesn't bring up phlegm, or mucus
- Wheezing
- Pain in the middle of the chest that gets worse when breathing deeply or coughing (rare).

However as only in advanced cases will the oxygen levels be reduced by exercise the level of disability due to pulmonary sarcoidosis itself, in the majority of patients means significant disability is unlikely.

Where the patient is requiring treatment for more advanced or symptomatic disease any disability is likely to arise either from the treatment or any extra pulmonary manifestation of the disease.

Sarcoidosis may cause general symptoms, including:

- Uneasiness, feeling sick (malaise), an overall feeling of ill health
- Tiredness, fatigue, weakness
- Loss of appetite or weight
- Fever
- Night sweats
- Sleep problems

Non - Respiratory

*Ocular involvement* occurs in 25% of cases with uveitis being the most common manifestation causing blurred vision and photobia.

*Arthritis* is reported in 25 – 50% with ankle, knee, wrist and elbow involvement being most common. Chronic arthritis can occur.

*Skin involvement* may cause itching, tender nodules (erythema nodosum) or sores on the nose, nasal passages, cheeks, ears, eyelids, and fingers in lupus pernio.

While most other systems (including gastro-intestinal, bone, neurological renal and cardiac can be involved in general they are relatively rare (5%) and their effects have to be considered on an individual basis.
Appendix A  Management of non-respiratory TB

Meningeal TB

Patients with active meningeal TB should be offered:
- a treatment regimen, initially lasting for 12 months, comprising isoniazid, pyrazinamide, rifampicin and a fourth drug (for example, ethambutol) for the first 2 months, followed by isoniazid and rifampicin for the rest of the treatment period
- a glucocorticoid at the normal dose range
  - adults – equivalent to prednisolone 20–40 mg if on rifampicin, otherwise 10–20 mg
  - children – equivalent to prednisolone 1–2 mg/kg, maximum 40 mg
- with gradual withdrawal of the glucocorticoid considered, starting within 2–3 weeks of initiation.

Clinicians prescribing treatment for active meningeal TB should consider as first choice:
- a daily dosing schedule
- using combination tablets

Peripheral lymph node TB

For patients with active peripheral lymph node tuberculosis, the first choice of treatment should be the standard recommended regimen:
- use a daily dosing schedule
- include combination tablets

Patients with active peripheral lymph node TB who have had an affected gland surgically removed should still be treated with the standard recommended regimen.

Drug treatment of peripheral lymph node TB should normally be stopped after 6 months, regardless of the appearance of new nodes, residual nodes or sinuses draining during treatment.

Bone and joint TB: drug treatment

The standard recommended regimen should be planned and started in people with:
- active spinal TB
- active TB at other bone and joint sites

Clinicians prescribing treatment for active bone and joint tuberculosis should consider as first choice:
- a daily dosing schedule
- using combination tablets
A computed tomography (CT) or magnetic resonance (MR) scan should be performed on patients with active spinal TB who have neurological signs or symptoms. If there is direct spinal cord involvement (for example, a spinal cord tuberculoma), management should be as for meningeal TB.

**Bone and joint TB: routine therapeutic surgery**

In patients with spinal TB, anterior spinal fusion should not be performed routinely. In patients with spinal TB, anterior spinal fusion should be considered if there is spinal instability or evidence of spinal cord compression.

**Pericardial TB**

For patients with active pericardial TB, the first choice of treatment should be:

- the standard recommended regimen use a daily dosing schedule include combination tablets

In addition to anti-TB treatment, patients with active pericardial TB should be offered:

- for adults, a glucocorticoid equivalent to prednisolone at 60 mg/day
- for children, a glucocorticoid equivalent to prednisolone 1mg/kg/day (maximum 40 mg/day)

with gradual withdrawal of the glucocorticoid considered, starting within 2–3 weeks of initiation.

**Disseminated (including miliary) TB**

For patients with disseminated (including miliary) TB, the first choice of treatment should be the standard recommended regimen use a daily dosing schedule include combination tablets

Treatment of disseminated (including miliary) TB should be started even if initial liver function tests are abnormal. If the patient's liver function deteriorates significantly on drug treatment, advice on management options should be sought from clinicians with specialist experience of these circumstances.

Patients with disseminated (including miliary) TB should be tested for central nervous system (CNS) involvement by:

- brain scan (CT or MRI) and/or lumbar puncture for those with CNS signs or symptoms
- lumbar puncture for those without CNS signs and symptoms.

If evidence of CNS involvement is detected, treatment should be the same as for meningeal TB.
Other sites of infection
For patients with:
  active genitourinary TB, or
  active TB of any site other than:
  • respiratory system
  • CNS (typically meninges)
  • peripheral lymph nodes
  • bones and joints
  • pericardium
  • disseminated (including miliary) disease
the first choice of treatment should be the standard recommended regimen
  use a daily dosing schedule
  include combination tablets
References

1 Health Protection Agency
2 Department of Health
3 Merck Manual
4 NICE Guidelines 033 Clinical diagnosis and management of tuberculosis, and measures for its prevention and control March 2006
5 Oxford Textbook of Medicine