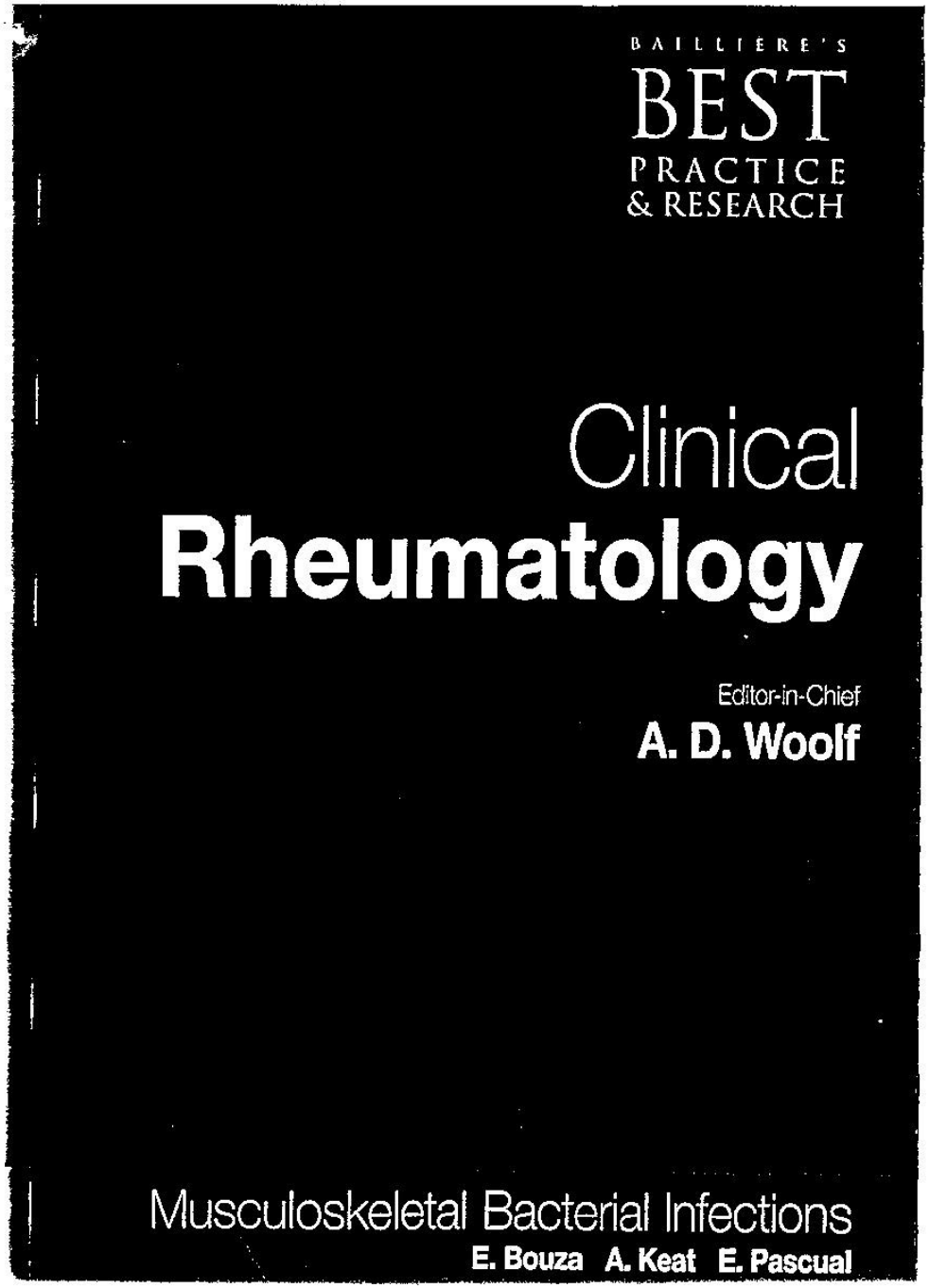
Skeletal tuberculosis and other granulomatous infections



Baillière's Clinical Rheumatology
Vol. 13, No. 1, pp 163–177, 1999

10

Skeletal tuberculosis and other granulomatous infections

Franco Paradisi MD
Professor and Chairman

Giampaolo Corti MD
Assistant Infectivologist

Infectious Disease Unit, University of Florence School of Medicine, Florence, Italy

After several decades of steadily decreasing incidence, tuberculosis has had a resurgence in the past 15 years, not only in the lungs, but also in extrapulmonary sites. This is primarily a result of the AIDS pandemic, considering that HIV specifically affects cellular immunity, which is the first-line defence against tuberculosis. The generally non-specific clinical and radiological patterns of skeletal tuberculosis make it similar to other bacterial, fungal, inflammatory and neoplastic diseases of the bones and joints. Physicians must not omit tuberculosis in the differential diagnosis of any osteo-articular inflammatory process so that specific treatment may be initiated as soon as possible. Anti-tuberculous therapy is beset by important factors that limit its efficacy, such as the emergence of drug toxicity and of resistant or multiresistant mycobacterial strains. Surgical treatment may be indicated in selected cases where medical therapy alone is not sufficient to eradicate the problem.

Key words: arthritis; atypical mycobacteria; brucellosis; drug resistance; drug therapy; fungal infections; *Mycobacterium tuberculosis*; osteomyelitis; spondylitis; tuberculosis.

NEW INDICATORS FOR AN OLD DISEASE

Tuberculosis (TB) was a frequent and lethal disease prior to the development of antibiotics, but since the 1950s there has been a steady decrease in its incidence. The resurgence of TB observed since the mid-1980s has been attributed primarily to the human immunodeficiency virus (HIV) epidemic and secondarily to other underlying diseases (diabetes mellitus, chronic renal failure, chronic obstructive pulmonary disease, liver cirrhosis, leukaemias and lymphomas). In addition, an ageing population, overcrowded prisons, social factors (alcohol and drug abuse, and homelessness) and immigration from developing countries (Hanza, 1994) all contribute to the problem. At the same time, some important features have in recent years appeared in industrialized countries, such as the concentration of TB in urban areas and the emergence of multidrug-resistant *Mycobacterium tuberculosis* strains (Centers for Disease Control and Prevention, 1998).

The increased frequency of TB involves both pulmonary and extrapulmonary sites. Among the latter, bone and joint deformities caused by spinal TB were a

1521–6942/99/010163 + 15 $12.00/00

concern in the ancient world, where strong evidence of their occurrence is documented in Egyptian mummies of the fourth millennium BC. Much more recently, the well-known 'white pestis' was carefully studied by Pott in the 18th century and by Poncet in the 19th. Today, skeletal involvement occurs in 1–5% of all TB patients (Pertuiset et al, 1997), and it is the fourth most common extrapulmonary localization of TB (Mehta et al, 1991). In developing countries, skeletal TB appears to be more common in children, whereas in industrialized nations adults are principally affected. No predilection for either sex has been observed (Lee and Abramson, 1996).

A pathogenetic and pathological view

It is generally accepted that skeletal TB results from the haematogenous dissemination of tubercle bacilli from a primary focus, earlier in children and later in adults. Alternatively, bacilli can spread by lymphatic drainage from an adjacent affected area such as the pleura or a kidney. Trauma can be considered to be a predisposing factor because skeletal TB most frequently involves weight-bearing joints and up to 50% of patients give a history of trauma (Kosinski and Smith, 1996).

Tubercles surrounded by normal tissue and containing central caseating necrosis, multinucleated giant cells, epithelioid cells and peripheral lymphocytes are the classical basic lesions termed 'caseating granulomas'. The inflammatory reaction, with the formation of granulation tissue, gradually leads to cartilage and eventually bone destruction, progressive demineralization, fibrosis and a resulting ankylosis. Paraosseous abscesses (so-called 'cold abscesses'), erosion and sinus tract formation may also develop (Yao and Sartoris, 1995).

CLINICAL AND RADIOLOGICAL MANIFESTATIONS

The early diagnosis and prompt treatment of skeletal TB are of fundamental importance in preventing severe bone and joint deformities. A delay between the initial symptoms and the aetiological diagnosis is possibly caused by a number of factors, for example the low incidence of skeletal TB, medical unawareness of this disease and the slow development of both the clinical and the radiological picture.

Typically, skeletal TB is a chronic and insidious mono-osteo-articular infection. Multiple site involvement is uncommon, being responsible for fewer than 30% of all cases. Local pain is the most common complaint, generally accompanied by joint and bone swelling and impairment of motion. Systemic symptoms such as low-grade fever, night sweats, anorexia and weight loss may or may not be present (Bernard and Perronne, 1997).

Vertebral TB (Pott's disease)

The vertebral column is affected in about 50% of all cases of skeletal TB, more often in the thoracic and lumbar regions. Typically, multiple vertebral bodies and disc spaces are involved, resulting in pain, limitation of motion and, in the late phases, severe spinal deformity (gibbus) attributed to an acute kyphotic angulation. Neurological complications such as paraplegia can occur in both the acute and late stages as a result of oedema and vascular engorgement. The transverse or spinous processes are infrequently involved (Lindahl et al, 1996), but the pedicles and laminae are affected more commonly than was previously suspected (Hoffman et al, 1993).

The radiological findings, summarized in Table 1, provide helpful diagnostic, although not pathognomonic, information. Later in the clinical course, lytic lesions are the radiological markers of Pott's disease, but sclerotic lesions may also occur.

During the past two decades, further information has been derived from both computed tomography (CT) and magnetic resonance imaging (MRI). CT is of great importance in revealing small, early infectious foci, the shape and calcification of a paravertebral abscess and the global extent of the lytic process (Jain et al, 1993), and in obtaining CT-guided needle aspiration specimens for both culture and histological diagnosis. MRI is mostly useful in delineating soft tissue swelling, because of its multiplanar capability and superior resolution, and in evaluating intramedullary lesions. The characteristic findings of MRI in vertebral TB include a decreased signal intensity on T1-weighted images of both vertebral bodies and disc spaces, but a signal intensity that is increased in the vertebral disc and markedly decreased in the vertebral bodies on T2-weighted images (Van de Kelft et al, 1992). The main disadvantage of MRI in this field is the difficulty of demonstrating cortical bone involvement and calcification within the paravertebral abscess.

Nuclear medicine imaging can detect a small focus of bone infection as a hot spot in the initial stages of vertebral TB, but in the case of bone destruction, scans with ^{99}technetium, ^{67}gallium and ^{111}indium are often negative (Watts and Lifeso, 1996).

The differential diagnosis of vertebral TB includes trauma, primary and metastatic tumours, osteoporotic fractures, pyogenic infections (brucellar, other bacterial and fungal) and sarcoidosis. Radiographic differentiation can be difficult but is sometimes feasible. For example, a reduced height of an intervertebral disc is only rarely seen in neoplastic forms, whereas a rapid loss of height in the disc, along with extensive sclerosis, the absence of gibbus deformities and the absence or minimal presence of calcified paravertebral masses, are suggestive of a pyogenic spine infection.

Table 1. Radiological changes in Pott's disease.

Early stages
Resorption of the dense margins of the end-plates and their demineralization
Narrowing or obliteration of the disc space
Soft tissue swelling (paravertebral abscess)
Late stages
Lytic progressive destruction of the anterior vertebral body
Anterior wedging
Vertebral collapse
Kyphotic deformities

TB osteomyelitis at other sites

This form of osteo-articular TB is generally caused by haematogenous spread and more rarely by the lymphatic or local extension of contiguous foci. Single involvement of the metaphysis of long bones such as femur, tibia and ulna, as well as of the small bones of hand and foot, is common. TB is the second most common destructive lesion of the ribs after metastatic neoplasia. The mastoid, mandible and skull are rare sites for TB osteomyelitis. Painful or sometimes painless swelling,

contiguous sinus tracts and cold soft tissue abscesses are typically reported (Lee and Abramson, 1996).

Traditional imaging techniques reveal osteopenia and osteolytic foci, so diagnosis is often delayed because this radiological picture is highly suggestive of primary or secondary neoplasia. Peripheral sclerosis, soft tissue swelling and periostitis are also shown on X-ray (Wright et al, 1996).

Tuberculous arthritis

TB of the joints is generally monoarticular and is facilitated by trauma, severe underlying diseases, a history of drug abuse, and intra-articular steroid injection. Weight-bearing joints such as the hips and knees, as well as the ankles and joints of the feet, are usually affected, whereas among the non-weight-bearing joints, involvement of elbows, wrists, joints of the hands and shoulders is prevalent. The clinical picture consists of classical manifestations such as pain, limitation of motion, weakness, joint swelling, chronic sinus formation, peri-articular abscess and, more rarely, systemic symptoms (low-grade fever, fatigue and weight loss) (Kramer and Rosenstein, 1997).

Early in the clinical course, conventional radiology may show only soft tissue and joint swelling with effusion. Later on, peri-articular osteopenia and the so-called Phemister's triad (peripheral osseous erosions, articular destruction with narrowing of the joint space and juxta-articular osteoporosis) take place. Nuclear medicine imaging can be helpful in the initial phases, whereas CT and MRI readily demonstrate peri-articular abscesses (Hugosson et al, 1996).

HOW TO MAKE A DIAGNOSIS

General indicators of inflammation, such as the measurement of the erythrocyte sedimentation rate and C-reactive protein level are non-specific and therefore not reliable for the ultimate diagnosis of skeletal TB. Radiographic features may be suggestive of bone or joint TB, but they are not mandatory. The tuberculin skin test is of limited value: a positive result supports the diagnosis, but a negative result does not exclude TB (Watts and Lifeso, 1996).

Microbiological and/or histological techniques are required for the final diagnosis of skeletal TB. A CT-guided needle aspiration, or sometimes an open biopsy, can provide adequate vertebral specimens for culture diagnosis, and the histopathological diagnosis is made in the presence of caseating granulomas (Rezai et al, 1996).

Unfortunately, Ziehl–Nielsen staining is positive in a minority of cases, and excess time is often required before culture results are known. In this context, the examination of clinical samples by molecular biology techniques can save time in order to initiate specific treatment as soon as possible. Nowadays, the use of the polymerase chain reaction (PCR) for the amplification of mycobacterial nucleic acids greatly shortens the time required for diagnosis to 1–2 days and yields a sensitivity and specificity close to 100%. The importance of PCR techniques is magnified in paucibacillary infections or in subjects with atypical presentations (Richeldi et al, 1995).

Synovial fluid aspiration and synovial biopsy are fundamental for the diagnosis of joint TB. The synovial fluid is usually non-haemorrhagic, turbid, and xanthocromic because of an elevated white blood cell count, which usually ranges between 10 000 and 20 000 cells per cubic millimetre with a polymorphonuclear leukocyte predominance. A high protein concentration and a low glucose level are other findings in tuberculous synovial fluid. Ziehl–Nielsen staining yields only a 20% positivity, whereas culture is positive in approximately 80% of cases (Lee and Abramson, 1996). Synovial biopsy is positive for typical caseating granulomas in more than 80% of patients (Sant and Bajaj, 1992). If bacteriology is negative and histology demonstrates only non-caseating granulomas, the differential diagnosis from other granulomatous diseases, such as sarcoidosis, brucellosis, infections caused by fungi or atypical mycobacteria, foreign-body giant-cell reaction and gout, can be difficult.

THERAPEUTIC APPROACH

The treatment of TB is primarily medical, based on the long-term administration of multidrug regimens in order to prevent the emergence of resistant strains. Surgical intervention may be an important adjunct in selected patients who meet the criteria.

The problem of drug resistance

Drug resistance (DR) and, more recently, multidrug resistance (MDR)—the latter defined as resistance to the two most important anti-TB agents, isoniazid and rifampicin, with or without resistance to other drugs—are of great concern in the management of patients with TB of any body site.

The drug resistance of *M. tuberculosis* is the result of a mixture of both human error and natural spontaneity. Treatment with a single agent because of either the physician's mistake or the patient's poor compliance, suppresses the growth of susceptible strains on the one hand, while facilitating the multiplication and spread of resistant strains on the other; this phenomenon is called 'acquired resistance'. The transmission of resistant strains to newly infected patients who fall ill with TB that is drug resistant from the beginning is known as 'primary resistance'.

The most recent data from 35 countries in five continents show that, in the case of TB, DR is ubiquitous, and MDR is the result of therapeutic anarchy. The prevalence of DR and MDR has a median value of 10.4% and 1.4% respectively for primary resistance, and 36% and 13% for acquired resistance, with a higher prevalence of both DR and MDR in countries with poor TB control programmes (WHO, 1998).

The problem of MDR TB is particularly important in HIV-infected patients, in whom severe nosocomial outbreaks have occurred both in the USA and in Europe (Alland et al, 1994; Herrera et al, 1996), because of the depletion of $CD4^+$ lymphocytes and other cellular immunity effectors involved in the defence against TB (Gordin et al, 1996). An important repercussion of MDR TB is that second- and/or third-line anti-TB agents—much more toxic and expensive—must be used.

Anti-tuberculous chemotherapy

Physicians have a number of effective drugs at their disposal for the therapy of TB (Table 2). Isoniazid, the most potent single mycobactericidal agent, must be administered at the daily dose of 5 mg/kg body weight (generally 300 mg per day). At this dosage, it is relatively safe. Major side-effects include hepatic toxicity, primarily

Table 2. A list of anti-tuberculous drugs.

Major oral drugs	*Parenteral drugs*
Isoniazid	Streptomycin (major)
Rifampicin	Amikacin
Pyrazinamide	Kanamycin
Ethambutol	Capreomycin
Minor oral drugs	
Ciprofloxacin	
Ofloxacin	
Ethionamide	
Cycloserine	
Aminosalicylic acid	

seen in slow acetylators, and peripheral neuropathy, preventable with oral pyridoxine substitution.

Rifampicin and pyrazinamide are other major mycobactericidal drugs. The usual doses are 10 mg/kg per day (generally 600 mg per day) and 20–30 mg/kg per day respectively, the most common undesirable reactions being gastrointestinal disturbance and jaundice for rifampicin, and arthralgia and hepatic toxicity for pyrazinamide.

Ethambutol is the only major anti-TB agent that is bacteriostatic. It is used in a dose of 15–25 mg/kg per day. Retrobulbar neuritis, evidenced by blurred vision and central scotoma, is the most serious adverse effect and is typically dose related.

Streptomycin is bactericidal but must be given intramuscularly in a dose of 15 mg/kg per day (maximum 1 g per day). Its best-known most frequent adverse effect is ototoxicity, especially in patients with renal failure.

Among the minor anti-TB drugs, amikacin and the more toxic kanamycin are aminoglycoside agents that may be used instead of streptomycin, at the same dosage (15 mg/kg per day). The new quinolones ciprofloxacin and ofloxacin are active in vitro against *M. tuberculosis* and draw scientists' attention as valid alternatives to major anti-TB drugs in cases of either toxicity or emerging resistance, being given at doses of 750 mg twice daily and 400 mg twice daily respectively. Ethionamide is the least tolerated among the anti-TB agents, with its universal gastrointestinal toxicity (abdominal pain, diarrhoea and metallic taste), and cycloserine is associated with important neuropsychic toxicity; both are administered in a dose of 250 mg two or three times a day. Other oral drugs display a modest microbiological (amithiozone, amoxicillin–clavulanate, azithromycin and clarithromycin) or clinical (clofazimine and rifabutin) efficacy (Alford and Wallace, 1995; Paradisi, 1996).

As for their pharmacokinetic properties, rifampicin and fluoroquinolones are known to diffuse well into bone and joint tissues, and consequently to achieve adequate local concentrations, whereas the osteo-articular penetration of other anti-TB agents is unknown. On this basis, fluoroquinolones can be considered to be the first-line alternatives to major oral anti-TB drugs for the treatment of skeletal TB.

Currently, a triple-drug regimen including isoniazid, rifampicin and pyrazinamide is recommended for the initial therapy of any type of TB. A fourth agent, for example ethambutol or streptomycin, is generally added if drug resistance is suspected, as with HIV-infected patients, or in the case of systemic or nervous involvement. Pyrazinamide and, if there is one, any fourth agent must be continued until the results of drug susceptibility tests are available, generally throughout the first 2 months.

The total duration of therapy is still a matter of debate. The short-course regimens of 6–9 months classically recommended for pulmonary TB may not be applicable to some extrapulmonary localizations such as the osteo-articular sites, especially if the clinical picture is severe or prolonged or the patient is infected by an MDR strain, which frequently occurs in subjects co-infected with or at high risk of HIV (e.g., intravenous drug abusers) or coming from endemic areas. In these cases, extending therapy to 12, 18 or even 24 months is usually indicated (Ad Hoc Committee, 1995; De Cock et al, 1995). In contrast, uncomplicated skeletal TB in HIV-negative subjects most often benefits from a 6–9-month course containing drugs with high sterilizing activity such as isoniazid and rifampicin (Medical Research Council, 1993; Meier and Beekmann, 1995).

Strict clinical and laboratory monitoring is required in order to avoid toxicity from multidrug anti-TB therapy. Bi-monthly monitoring of serum transaminase values is needed because of the liver toxicity caused by isoniazid, rifampicin and, to a lesser extent, pyrazinamide. Other laboratory parameters to be checked include plasma urate levels, often increased by pyrazinamide, and creatinine values, affected by aminoglycosides other than streptomycin. At the clinical level, it is important to verify the possible emergence of retrobulbar neuritis caused by ethambutol or the dizziness or hearing loss attributable to streptomycin.

In the case of proven MDR TB, drug regimens including 4–6 anti-TB agents must be initiated in the hospital setting in order to control the possible emergence of drug toxicity. A list of therapeutic strategies for patients with MDR TB is shown in Table 3 (Iseman, 1993).

In patients with a clinical and radiological picture suggestive of skeletal TB, but without any bacteriological and/or histological evidence of the infection, the problem arises of whether or not anti-TB therapy should be initiated. If microbiological studies for other bacteria and fungi and serological tests for sarcoidosis are negative, and a diagnosis of gout or metastatic bone neoplasia can be excluded, we believe that an empirical anti-TB treatment can be started, monitoring both clinical response and laboratory indicators of drug toxicity. If no clinical improvement has been observed by the third month of therapy, treatment must be stopped and another diagnosis sought.

Table 3. Anti-mycobacterial regimens for the treatment of drug-resistant tuberculosis.

Resistance to	Regimen	Duration of therapy
Isoniazid, streptomycin, pyrazinamide	Rifampicin, ethambutol, ciprofloxacin orofloxacin, amikacin or capreomycin	6–9 months
Isoniazid, ethambutol (±streptomycin)	Rifampicin, pyrazinamide, ciprofloxacin orofloxacin, amikacin	6–12 months
Isoniazid, rifampicin (±streptomycin)	Pyrazinamide, ethambutol, ciprofloxacin or ofloxacin, amikacin	18–24 months
Isoniazid, rifampicin, ethambutol (±streptomycin)	Pyrazinamide, ciprofloxacin or ofloxacin, amikacin plus two other drugs*	2 years after culture has become negative
Isoniazid, rifampicin pyrazinamide (±streptomycin)	Ethambutol, ciprofloxacin or ofloxacin, amikacin plus two other drugs*	2 years after culture has become negative
Isoniazid, rifampicin, ethambutol, pyrazinamide (±streptomycin)	Ciprofloxacin or ofloxacin, amikacin plus three other drugs*	2 years after culture has become negative

* Choose between ethionamide, cycloserine and aminosalicylic acid.

We recently observed a 50-year-old Caucasian woman with a 2-year history of pain and swelling localized to the left knee and limitation of motion, whose X-ray findings showed Phemister's triad. Synovial fluid analysis yielded only non-specific findings, and both Ziehl–Nielsen staining and culture were negative. Other diseases could be excluded on clinical, radiological, and serological levels, so we initiated a three-drug (isoniazid–rifampicin–pyrazinamide) anti-TB regimen, which has been well tolerated during its first 2 months. At the present time, the patient's complaints are reduced, strengthening our empirical diagnosis.

Surgery and other therapeutic measures

Indications for surgical treatment as an adjunct to chemotherapy primarily include unresponsiveness to and non-compliance with medical therapy, the presence of a large or otherwise undrainable abscess and, in the case of vertebral TB, the development of neurological abnormalities (acute deterioration, paraparesis or paraplegia) and/or spinal instability or deformity of more than 5 degrees. In the surgical correction of Pott's disease, the most frequent procedures provide for a posterior (laminectomy), posterolateral (costotransversectomy) or anterior approach. As an adjunct to medical therapy in subjects with vertebral TB, some authors advise using external bracing for 6–12 months if patients have undergone surgery, and 12–18 months if they have not (Rezai et al, 1996). The efficacy of this measure is debatable, and other researchers have stated that no benefits accrue from plaster jackets or minor surgical procedures (Jellis, 1995).

In articular TB, operative intervention includes excisional arthroplasty (hip and elbow) and arthrodesis (knee, shoulder, ankle and wrist) (Jellis, 1995).

SKELETAL GRANULOMATOUS INFECTION CAUSED BY OTHER MYCOBACTERIA

Atypical mycobacteria determine bone and joint disease, mostly in immunocompromised patients with pre-existing conditions such as malignancy or AIDS or on corticosteroid therapy. Infection usually derives from either haematogenous spread or percutaneous inoculation and generally involves the small long bones (the digits), the tendon sheaths of the upper limbs, bursae or the joints (wrist and knee). In immunocompetent subjects, atypical mycobacterial infections are rare and very like skeletal TB on both clinical and radiological grounds. The clinical picture consists of local pain and constitutional symptoms such as low-grade fever and weight loss, the radiographic findings including multiple involvement of the metaphyses and diaphyses of long bones, lytic areas, sclerosis and osteoporosis (Wolinsky, 1992).

In patients with HIV infection, atypical mycobacterial skeletal infections generally occur at advanced stages of the disease, mostly when the $CD4^+$ count is lower than 100 cells/mm^3. They often produce multiple site involvement, a concomitant skin infection and/or dissemination of infection (Hirsch et al, 1996). The diagnosis is usually established by culture isolation of the organism from biopsy tissue or synovial fluid. The average time for growth is generally 20–30 days, but a significant shortening to 5–12 days is achievable using liquid (broth) media (BACTEC®, Becton Dickinson Diagnostic Instrument Systems, Towson, USA). The diagnosis of atypical mycobacterial infections is now more rapid, although more complex and expensive, because of the development of new techniques allowing the identification of mycobacterial colonies on solid media within a few hours (chemiluminescent DNA probes and gas–liquid and high-performance liquid chromatography) (Woods, 1994). Moreover, the identification of mycobacteria from tissue specimens is feasible by either latex agglutination or DNA amplification (PCR) (Reischl and Naumann, 1996).

Mycobacterium avium intracellulare (MAC), *M. chelonei*, *M. fortuitum*, *M. haemophilum* and *M. kansasii* most commonly cause skeletal infections, generally through penetrating injuries. MAC is more frequently responsible for tenosynovitis and less commonly arthritis, bursitis and osteomyelitis (Kiely et al, 1995). It is resistant to both isoniazid and pyrazinamide, so combination therapy must include a new macrolide (clarithromycin or azithromycin), ethambutol and generally a third drug to be chosen from rifampicin (or rifabutin), ciprofloxacin, amikacin and clofazimine, as in HIV-infected patients with disseminated MAC infection (Benson, 1994).

The other above-mentioned mycobacteria generally cause osteomyelitis and arthritis in immunocompromised subjects such as AIDS patients. Therapy for *M. chelonei* and *M. fortuitum* infections is very difficult because of their resistance to all conventional anti-TB drugs, so alternative agents must be used, for example an aminoglycoside (amikacin) associated with clarithromycin (*M. chelonei*) or with cefoxitin, ciprofloxacin or a tetracycline (*M. fortuitum*) (French et al, 1997). *Mycobacterium haemophilum* must be considered to be an emerging pathogen; rifampicin, amikacin and ciprofloxacin seem to be effective against it both in vitro and in vivo, albeit anecdotally (Straus et al, 1994). *Mycobacterium kansasii* infection responds well to the classical anti-TB combination of isoniazid, rifampicin and ethambutol for at least 18 months (Witzig et al, 1995).

OTHER GRANULOMATOUS INFECTIONS OF BONES AND JOINTS

Brucellosis

Bacteria of the genus *Brucella* have different host animals, for example goats, sheep and camels (*B. melitensis*), cattle (*B. abortus*), swine (*B. suis*) and dogs (*B. canis*). Although they usually cause a systemic disease characterized by the classic triad of fever, arthralgia and hepatosplenomegaly, primary osteo-articular involvement has been documented as the most frequent focal complication (in up to 80% of all cases), mainly in endemic areas such as the Mediterranean basin, the Middle East and Latin America. Large joint arthritis, unilateral sacroiliitis and lumbar spondylitis (pseudo-Pott's disease) are, in decreasing order of frequency, the most common osteo-articular manifestations of brucellosis, osteomyelitis, bursitis and tenosynovitis being infrequently reported. An abrupt onset of spontaneous pain, painful limitation of movement and difficulty in walking and even standing is typical of sacroiliitis, whereas an insidious and chronic course is more often observed in spondylitis, in which narrowing of the disc space, end-plate and body destruction, bony sclerosis, spondylolysis and spondylolisthesis are characteristically seen on a standard X-ray. CT scans better define vertebral involvement with bone sclerosis, vertebral arch destruction and paravertebral abscess formation, whereas nuclear medicine imaging (^{99}technetium scanning) is more sensitive in demonstrating acute sacroiliitis and other osteo-articular lesions (Rajapakse, 1995).

Traditional diagnostic tools include culture isolation from tissues or, less invasively, from blood (after a 3-week or longer incubation culture because brucellae grow slowly), and serological methods, of which the serum agglutination test (SAT) is the most widely used (a four-fold rise in antibody titre between the acute and convalescent phase samples being mandatory for diagnosis). As these procedures are time consuming, alternative techniques have therefore been investigated and developed for the fast detection of infection. With automated blood culture systems such as BACTEC®, the isolation time is greatly reduced, the vast majority of bacterial strains being detected within 5 days (Bannatyne et al, 1997). Single-step peripheral-blood PCR assay has both sensitivity and specificity values close to 100% and provides results within a few hours (Queipo-Ortuño et al, 1997), although it is not available in most clinical laboratories. Newer enzyme immune assays (ELISA) seem to be very promising, whereas the rose bengal test, a rapid latex agglutination method so simple that it can be carried out in the doctor's surgery, has values for sensitivity and specificity higher than 95% and a good correlation with the SAT (Colmenero et al, 1989).

Histological appearances are not pathognomonic, showing non-specific non-caseating granulomas.

In the differential diagnosis between tuberculous and brucellar spondylitis, a striking contrast between pain (severe in TB and less prominent in brucellosis) and bone destruction (more evident in brucellosis) has been observed.

Although many antimicrobial agents are active in vitro against *Brucella* spp., susceptibility tests do not correlate with clinical efficacy as brucellae are facultative intracellular pathogens. Antibiotic treatment with tetracycline 500 mg four times a day (or doxycycline 100 mg twice daily) for 6 weeks is the cornerstone of medical treatment for brucellosis, including osteo-articular localizations (Paradisi, 1996). The combination with either streptomycin 1 g per day for 15 days or rifampicin 600–900 mg per day for 6 weeks is needed because monotherapy is associated with significantly higher relapse rates (Young, 1995). Whereas some researchers have found no difference among several combinations including tetracycline (or doxycycline) plus streptomycin (or rifampicin) with regard to the early clinical response in human brucellosis (Malik, 1998), other authors have reported the significantly higher efficacy of a doxycycline–streptomycin than a doxycycline–rifampicin regimen in terms of both early clinical response and lack of relapse, primarily in patients with brucellar spondylitis (Solera et al, 1995). In intolerant subjects, pregnant women and children, co-trimoxazole 960 mg twice daily is a valid alternative to tetracycline, whether it is used in association with rifampicin for 6 weeks or alone; in the latter case, prolonging therapy to 3–6 months is required. The fluoroquinolones ciprofloxacin and especially ofloxacin are highly active in vitro against *Brucella* spp. and penetrate intracellularly very well, but relapse rates as high as 66% have been reported when they have been used alone. Although the combination of ofloxacin with rifampicin is as effective as a doxycycline–rifampicin regimen, it is not recommended that fluoroquinolones replace standard tetracycline–aminoglycoside (or –rifampicin) therapy (Solera et al, 1997). Indications for surgical treatment are the same as for skeletal TB.

Fungal infections

As in the case of atypical mycobacterial infections, fungal involvement of the bones and joints is usually observed in immunocompromised patients as the result of a number of factors, for example HIV infection, diabetes mellitus, haematological neoplasia, bone marrow transplantation and immunosuppressive or cytotoxic therapy (Meier and Beekmann, 1995).

Many fungi have been reported to cause osteo-articular infection, usually by haematogenous spread: *Candida albicans* and other non-*C. albicans* candida (*C. krusei* and *Torulopsis glabrata*), *Aspergillus flavus*, *Saccharomyces* spp., *Actinomyces* spp., *Cryptococcus neoformans* and *Mucorales* spp., are all seen. The importance of other fungal agents (*Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides immitis* and *Paracoccidioides parabraziliensis*) lies in their endemic nature. Mycotic spondylitis presents with a clinical (pain and fever) and radiological (lytic lesions, involvement of the anterior end-plates and soft tissue extension) picture resembling that of Pott's disease; fungal osteomyelitis of other sites such as the long bones, jaws and feet has been reported (Adkins et al, 1994; Gurevitz et al, 1994; Lagging et al, 1994; Lasday and Jay, 1994; Shaw et al, 1994; Hovi et al, 1996).

Arthritis is another osteo-articular manifestation of fungal infection, especially in patients who have undergone antibiotic or immunosuppressive therapy or the insertion of a joint prosthesis. Weight-bearing joints such as knees are usually affected, with complaints of warmth, tenderness and swelling, similar to the picture with TB arthritis (Hansen and Andersen, 1995).

The therapy of life-threatening infections and/or infections in immuno-compromised subjects is still based on amphotericin B at a daily dosage of 0.3–0.7 mg/kg (to a total maximal dose of 2.5 g). In non-life-threatening infections, including mild-to-moderate endemic mycoses (i.e. blastomycosis, coccidioidomycosis and histoplasmosis), the recently introduced oral azoles fluconazole and itraconazole can be used for a total duration of approximately 12 months, with a preference for itraconazole except in cryptococcal infections (Meier and Beekmann, 1995).

OTHER GRANULOMATOUS DISEASES OF BONE AND JOINTS

Sarcoidosis causes bone lesions in approximately 5% of patients, and more commonly joint disease, seen in 25–50% of cases. Sarcoid arthritis is generally polyarticular and affects the large joints, with transient, sometimes migratory, arthralgia. Bone lesions are prevalent in the hand and foot, and are initially tender and painful, but the advanced phases are characterized by extensive bone destruction with deformity. X-rays generally showing lytic lesions with cyst-like areas. Importantly, histopathological studies highlight the presence of non-caseating epithelioid granulomas similar to those of a number of bacterial and fungal infections, but the presence of skin anergy and the elevation of both serum angiotensin-converting enzyme and 24-hour urinary calcium levels are consistent with the diagnosis of sarcoidosis and indicate glucocorticoid therapy (Crystal, 1998).

Gouty arthritis is typically an acute monoarticular disease of peripheral joints, although peri-articular sites can be affected. Pain is severe and generally accompanied by tenderness, warmth, swelling and erythema. X-ray films typically show erosive lesions of the juxta-articular bone surrounded by sclerotic borders, and nodular soft-tissue prominence ('tophus') as a result of urate crystal deposition. Hyperuricaemia is an important but not infallible marker that facilitates the diagnosis of gout from that of

other inflammatory diseases of the joints (Wortmann, 1998), although the only absolute criterion for diagnosis remains the demonstration of urate crystals in the affected tissues.

SUMMARY

In sight of the third millennium, tuberculosis is still a serious public health problem not only in developing countries, but also even in industrialized nations, where new factors such as drug resistance and—what is more troubling—multidrug resistance have emerged. An osteo-articular localization, responsible for less than 5% of all tuberculous infections, is very rare; nevertheless, skeletal tuberculosis must be kept in mind in the differential diagnosis of patients with a clinical and radiological picture suggestive of either osteomyelitis or arthritis. In fact, there exist the risk of:

1. incorrect suspicion of other bone and joint granulomatous diseases such as atypical mycobacterial, brucellar and fungal infections, and chronic inflammatory illnesses (sarcoidosis and gout), as well as of primary and metastatic neoplasias;
2. a late initiation of anti-tuberculous therapy when significant deformities can have already occurred.

With the suspicion of skeletal tuberculosis, either needle aspiration or open biopsy should be carried out to provide material for both microbiological and histological studies. The newly introduced molecular biology methods can be helpful tools for an earlier diagnosis, the presence of caseating granulomas in histological preparations is pathognomonic, and drug susceptibility tests on the strain isolated from culture allow targeted treatment. Anti-mycobacterial therapy must be conducted with a three- or four-drug regimen for a prolonged period in order to avoid the emergence of resistant strains. Strict co-operation between four groups of specialist—orthopaedic surgeons/rheumatologists, infectious disease specialists, radiologists and microbiologists—is required for the correct and successful management of patients with osteo-articular tuberculosis.

Practice points

- the differential diagnosis of vertebral TB includes trauma, primary and metastatic tumours, osteoporotic fractures, pyogenic infections (brucellar, other bacterial and fungal) and sarcoidosis. Radiographic differentiation can be difficult but is sometimes feasible
- traditional imaging techniques reveal osteopenia and osteolytic foci, so diagnosis is often delayed because this radiological picture is highly suggestive of primary or secondary neoplasia
- if bacteriology is negative and histology demonstrates only non-caseating granulomas, the differential diagnosis from other granulomatous diseases, such as sarcoidosis, brucellosis, infections caused by fungi or atypical mycobacteria, foreign-body giant-cell reaction and gout, can be difficult
- strict clinical and laboratory monitoring is required in order to avoid toxicity from multidrug anti-TB therapy. Bi-monthly monitoring of serum transaminase values is needed because of liver toxicity (isoniazid, rifampicin and pyrazinamide). Other laboratory parameters to be checked include plasma urate levels (pyrazinamide) and creatinine values (aminoglycosides other than streptomycin). At the clinical level, it is important to verify the possible emergence of retrobulbar neuritis (ethambutol) or dizziness and hearing loss (streptomycin)
- in patients with a clinical and radiological picture suggestive of skeletal TB, but without any bacteriological and/or histological evidence of infection, the problem arises of whether or not anti-TB therapy should be initiated. If microbiological studies for other bacteria and fungi and serological tests for sarcoidosis are negative, and gout and metastatic bone neoplasia can be excluded, empirical anti-TB treatment can be started, monitoring clinical response and laboratory indicators of toxicity. If no clinical improvement has been observed by the third month, treatment must be stopped and another diagnosis sought
- in the differential diagnosis between tuberculous and brucellar spondylitis, a striking contrast between pain (TB) and bone destruction (brucellosis) has been observed

Research agenda

- the total duration of therapy is still a matter of debate. The short-course regimens of 6–9 months classically recommended for pulmonary TB may not be applicable to some extrapulmonary localizations such as the osteo-articular sites

REFERENCES

Ad Hoc Committee of the Scientific Assembly on Microbiology, Tuberculosis, and Pulmonary Infections (1995) Treatment of tuberculosis and tuberculosis infection in adults and children. *Clinical Infectious Diseases* **21:** 9–27.

Adkins T, Rees M, Simeone F et al (1994) Case records of the Department of Medicine University of Mississippi Medical Center. *Histoplasma capsulatum* osteomyelitis humerus, metastatic pulmonary histoplasmosis. *Journal of the Mississippi State Medical Association* **35:** 59–64.

Alford RH & Wallace RJ Jr (1995) Antimycobacterial agents. In Mandell GL, Bennett JE & Dolin R (eds) *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*, 4th edn, pp 389–400. New York: Churchill Livingstone.

Alland D, Kalkut GE, Moss AR et al (1994) Transmission of tuberculosis in New York City. An analysis by DNA fingerprinting and conventional epidemiologic methods. *New England Journal of Medicine* **330:** 1710–1716.

Bannatyne RM, Jackson MC & Memish Z (1997) Rapid diagnosis of *Brucella* bacteremia by using the BACTEC 9240 system. *Journal of Clinical Microbiology* **35:** 2673–2674.

Benson CA (1994) Treatment of disseminated disease due to the *Mycobacterium avium* complex in patients with AIDS. *Clinical Infectious Diseases* **18 (supplement 3):** S237–S242.

Bernard L & Perronne C (1997) La tuberculose ostéo-articulaire aujourd'hui. *Presse Médicale* **26:** 308–310.

Centers for Disease Control and Prevention (1998) Tuberculosis morbidity-United States, 1997. *Morbidity and Mortality Weekly Report* **47:** 253–257.

De Cock KM, Grant A & Porter JD (1995) Preventive therapy for tuberculosis in HIV-infected patients: international recommendations, research, and practice. *Lancet* **345:** 833–836.

Colmenero JD, Reguera JM, Cabrera FP et al (1989) Empleo combinado del rosa de Bengala e immunofluorescencia indirecta en el diagnostico de la brucelosis. *Enfermedades Infecciosas y Microbiologia Clinica* **7:** 316–320.

Crystal RG (1998) Sarcoidosis. In Fauci AS, Braunwald E, Isselbacher KJ et al (eds) *Harrison's Principles and Practice of Internal Medicine*, pp 1922–1928. New York: McGraw-Hill.

*French AL, Benator DA & Gordin FM (1997) Nontuberculous mycobacterial infections. *Medical Clinics of North America* **81:** 361–379.

Gordin FM, Nelson ET, Matts JP et al (1996) The impact of human immunodeficiency virus infection on drug resistant tuberculosis. *American Journal of Respiratory Critical Care Medicine* **154:** 1478–1483.

Gurevitz O, Goldschmied-Reuven A, Block C et al (1994) *Cryptococcus neoformans* vertebral osteomyelitis. *Journal of Medical and Veterinary Mycology* **32:** 315–318.

*Hansen BL & Andersen K (1995) Fungal arthritis. A review. *Scandinavian Journal of Rheumatology* **24:** 248–250.

*Hanza M (1994) Joint and spine tuberculosis. *Review of Rheumatology* **60:** 83–86.

Herrera D, Cano R, Godoy P et al (1996) Multidrug-resistant tuberculosis outbreak on an HIV ward—Madrid, Spain, 1991–1995. *Morbidity and Mortality Weekly Report* **45:** 330–333.

Hirsch R, Miller SM, Kazi S et al (1996) Human immunodeficiency virus-associated atypical mycobacterial skeletal infections. *Seminars in Arthritis and Rheumatism* **25:** 347–356.

Hoffman EB, Crosier JH & Cremin BJ (1993) Imaging in children with spinal tuberculosis. *Journal of Bone and Joint Surgery* **75:** 233–239.

Hovi L, Saarinen UM, Donner U & Lindqvist C (1996) Opportunistic osteomyelitis in the jaws of children on immunosuppressive chemotherapy. *Journal of Pediatric Hematology and Oncology* **18:** 90–94.

Hugosson C, Nyman RS, Brismar J et al (1996) Imaging of tuberculosis. V: Peripheral osteoarticular and soft-tissue tuberculosis. *Acta Radiologica* **37:** 512–516.

*Iseman MD (1993) Treatment of multidrug-resistant tuberculosis. *New England Journal of Medicine* **329:** 784–791.

Jain R, Sawhney S & Berry M (1993) Computed tomography of skeletal tuberculosis. *Clinical Radiology* **47:** 196–199.

Jellis JE (1995) Bacterial infections: bone and joint tuberculosis. *Baillière's Clinical Rheumatology* **9:** 151–159.

Van de Kelft E, Van Vyve M, Parizel PM et al (1992) MR imaging of tuberculous spondylitis. *Journal Belge de Radiologie* **75:** 202–204.

Kiely JL, O'Riordan DM, Sheehan S et al (1995) Tenosynovitis due to mycobacteria other than tuberculosis: a hazard of water sports and hobbies. *Respiratory Medicine* **89:** 69–71.

Kosinski MA & Smith LC (1996) Osteoarticular tuberculosis. *Clinical Podiatry in Medicine and Surgery* **13:** 725–739.

*Kramer N & Rosenstein ED (1997) Rheumatologic manifestations of tuberculosis. *Bulletin of Rheumatic Diseases* **46:** 5–8.

Lagging LM, Breland CM, Kannedy DJ et al (1994) Delayed treatment of pulmonary blastomycosis causing vertebral osteomyelitis, paraspinal abscess, and spinal cord compression. *Scandinavian Journal of Infectious Disease* **26:** 111–115.

Lasday SD & Jay RM (1994) Candida osteomyelitis. *Journal of Foot and Ankle Surgery* **33:** 173–176.

Lee SH & Abramson SB (1996) Infections of the musculoskeletal system by *M. tuberculosis*. In Rom WN & Garay S (eds) *Tuberculosis*, pp 635–644. Boston: Little, Brown.

Lindahl S, Nyman RS, Brismar J et al (1996) Imaging of tuberculosis. IV: Spinal manifestations in 63 patients. *Acta Radiologica* **37:** 506–511.

Malik GM (1998) Early clinical response to different therapeutic regimens for human brucellosis. *American Journal of Tropical Medicine and Hygiene* **58:** 190–191.

Medical Research Council, Working Party on Tuberculosis of the Spine, Twelfth Report (1993) Controlled trial of short-course regimens of chemotherapy in the ambulatory treatment of spinal tuberculosis: results at three years of study. *Journal of Bone and Joint Surgery British Volume* **75:** 240–248.

Mehta JB, Dutt A, Harvill L & Mathews KM (1991) Epidemiology of extrapulmonary tuberculosis. A comparative analysis with pre-AIDS era. *Chest* **99:** 1134–1138.

*Meier JL & Beekmann SE (1995) Mycobacterial and fungal infections of bone and joints. *Current Opinion in Rheumatology* **7:** 329–336.

Paradisi F (1996) *Terapia delle infezioni*, 3rd edn. Torino, Edizioni Minerva Medica.

Pertuiset E, Beaudreuil J, Horusitzky A et al (1997) Aspects épidémiologiques de la tuberculose ostéo-articulaire de l'adulte. *Presse Médicale* **26:** 311–315.

Queipo-Ortuño MI, Morata P, Ocón P et al (1997) Rapid diagnosis of human brucellosis by peripheral-blood PCR assay. *Journal of Clinical Microbiology* **35:** 2927–2930.

*Rajapakse CN (1995) Bacterial infections: osteoarticular brucellosis. *Baillière's Clinical Rheumatology* **9:** 161–177.

Reischl U & Naumann L (1996) Molekularbiologische methoden zum nachweis von mykobakterien. Verbesserte und neuentwickelte testsysteme zur mykobakteriendiagnostik. *Fortschritte der Medizin* **114:** 237–241.

Rezai AR, Lee M & Cooper PR (1996) Pott's disease. In Rom WN & Garay S (eds) *Tuberculosis*, pp 623–633. Boston: Little, Brown.

Richeldi L, Barnini S & Saltini C (1995) Molecular diagnosis of tuberculosis. *European Respiratory Journal* **20 (supplement):** 689S–700S.

Sant M & Bajaj H (1992) Role of histopathology in the diagnosis of tuberculous synovitis. *Journal of the Indian Medical Association* **90:** 263–264.

Shaw CJ, Thomason AJ & Spencer JD (1994) Fungal osteomyelitis of the foot. A report of an unusual case. *Journal of Bone and Joint Surgery British Volume* **76:** 137–139.

Solera J, Martínez-Alfaro E & Espinosa A (1997) Recognition and optimum treatment of brucellosis. *Drugs* **53:** 245–256.

Solera J, Rodríguez-Zapata M, Geijo P et al (1995) Doxycycline–rifampin versus doxycycline–streptomycin treatment of human brucellosis due to *Brucella melitensis*. *Antimicrobial Agents and Chemotherapy* **39:** 2061–2067.

Straus WL, Ostroff SM, Jernigan DB et al (1994) Clinical and epidemiologic characteristics of *Mycobacterium haemophilum*, an emerging pathogen in immunocompromised patients. *Annals of Internal Medicine* **120:** 118–125.

*Watts HG & Lifeso RM (1996) Tuberculosis of bone and joints. *Journal of Bone and Joint Surgery* **78A:** 288–298.

WHO Global Tuberculosis Programme (1998) *Anti-tuberculosis Drug Resistance in the World*. Geneva: WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance 1994–1997.

Witzig RS, Fazal BA, Mera RM et al (1995) Clinical manifestations and implications of coinfection with *Mycobacterium kansasii* and human immunodeficiency virus type 1. *Clinical Infectious Diseases* **21:** 77–85.

Wolinsky E (1992) Mycobacterial diseases other than tuberculosis. *Clinical Infectious Diseases* **15:** 1–12.

Woods GL (1994) Disease due to the *Mycobacterium avium* complex in patients infected with human immunodeficiency virus: diagnosis and susceptibility testing. *Clinical Infectious Diseases* **18 (supplement 3):** S227–S232.

Wortmann RL (1998) Gout and other disorders of purine metabolism. In Fauci AS, Braunwald E, Isselbacher KJ et al (eds) *Harrison's Principles and Practice of Internal Medicine*, pp 2158–2166. New York: McGraw-Hill.

Wright T, Sundaram M & McDonald D (1996) Radiologic case study. Tuberculous osteomyelitis and arthritis. *Orthopedics* **19:** 699–702.

*Yao DC & Sartoris DJ (1995) Musculoskeletal tuberculosis. *Radiologic Clinics of North America* **33:** 679–689.

Young EJ (1995) An overview of human brucellosis. *Clinical Infectious Diseases* **21:** 283–289.