

7

Disseminated infection, cervical adenitis and other MAC infections

C.F. von Reyn, A. Pozniak, W. Haas and G. Nichols

7.1 DISSEMINATED MAC INFECTION

7.1.1 Clinical aspects

Disseminated infection with organisms of the MAC was first recognized in immunocompromised patients, including those with hairy cell leukaemia or on steroid therapy (Horsburgh *et al.* 1985). Subsequently, disseminated MAC was identified as a common complication of advanced AIDS (Zakowski *et al.* 1982). Patients with disseminated MAC typically present with a chronic wasting illness characterized by several weeks of fever, night sweats, malaise and weight loss. Abdominal pain and diarrhoea may also be seen (Horsburgh 1991; Benson & Ellner 1993). Laboratory studies demonstrate anaemia in most patients and an elevated alkaline phosphatase in a minority (Havlik *et al.* 1992).

In AIDS patients, *M. avium* infection is acquired predominantly through the gastrointestinal tract where it is able to translocate the intestinal mucosa, infect and replicate in the submucosal macrophages, and cause bacteremia leading to dissemination of the organism (McGarvey & Bermudez 2001). Pathological studies show widespread distribution of organisms in the liver, spleen, bone marrow and gastrointestinal tract with 10^7 - 10^{10} cfu/gm of tissue. Renal involvement, possibly associated with nephrocalcinosis (Falkoff *et al.* 1987), and inflammation of the peritoneum have also been reported in AIDS patients with disseminated MAC infection (van der Reijden *et al.* 1989; Perazella *et al.* 1993).

A characteristic feature is the presence of numerous acid-fast staining organisms within foamy macrophages (Wong *et al.* 1985; Torriani *et al.* 1996). The high organism burden is associated with persistent bacteraemia and the diagnosis is typically confirmed by culture of blood or biopsy and staining of bone marrow, liver or small bowel.

Another clinical form of MAC disease has also been recognized in HIV infection. HIV-infected patients with previously unrecognized or subclinical *M. avium* infection may experience an immune reconstitution syndrome within two months of responding to HAART. This is a local inflammatory syndrome distinct from disseminated MAC. Clinical features include culture-positive lymphadenitis or other localized granulomatous disease, sometimes with draining sinuses, and negative blood cultures for mycobacteria (DeSimone *et al.* 2000).

7.1.2 Microbiology

Most blood isolates from HIV patients with disseminated MAC are *M. avium*. Early studies using serotyping methods indicated that a majority of these strains from the United States were serotype 4 or 8, with serotype 6 isolated from patients in Scandinavian countries (Hoffner *et al.* 1990; Tsang *et al.* 1992). More recent molecular studies have shown that *M. avium* strains isolated from blood represent phylogenetic lineages distinct from those among strains isolated from pulmonary sources or the environment (Smole *et al.* 2002). An interesting and unique feature of disseminated *M. avium* infection complicating AIDS is that as many as 25% of patients are infected simultaneously with two or more different strains (von Reyn *et al.* 1995). This implies that patients are either infected from exposure to mixed populations in a single environmental source or from multiple exposures to singular populations in different environmental sources.

7.1.3 Epidemiology and risk factors

Disseminated *M. avium* in HIV-negative people occurs primarily in patients with identifiable defects in cellular immunity. Cases have been described among patients with

familial immunodeficiencies (especially hereditary defects in IFN-gamma receptors), among patients with leukaemia (especially hairy cell leukaemia) and lymphoma, patients on steroid therapy, patients with collagen vascular disease, and among bone marrow and solid organ transplant recipients (Weinstein *et al.* 1981; Horsburgh *et al.* 1985; Bennett *et al.* 1986; Newport *et al.* 1996; Roy & Weisdorf 1997; Barcat *et al.* 1998; Nagy & Rubin 2001). Nonetheless, approximately 40% of HIV-negative patients with disseminated *M. avium* have no identifiable immune defect (Horsburgh *et al.* 1985).

Among AIDS patients, the risk of disseminated *M. avium* is related to the CD4 count and disease occurs predominantly among patients with CD4 counts less than 75-100/mm³. In a large cohort of AIDS patients the overall risk of disseminated *M. avium* was found to be approximately 20% per year. Stratified by CD4 count the risk is approximately 39% per year with a CD4 count of < 10, 30% for CD4 10-19, 20% for CD4 20-39, 15% for CD4 40-59, 8% for CD4 60-99 and 3% for CD4 100-199 (Nightingale *et al.* 1992).

Epidemiological studies indicate that the risk of disseminated *M. avium* in advanced AIDS is high in developed countries and low or absent in developing countries (e.g. sub-Saharan Africa) (von Reyn *et al.* 1996). It is not known if genetic factors or geographic differences in mycobacterial immunity or pathogenicity of *M. avium* stains may contribute to this difference. MAC are present in the African environment (von Reyn *et al.* 1993) and healthy African populations have significant rates of skin test reactivity to MAC antigens (von Reyn *et al.* 1993) suggesting that exposure to MAC does occur in developing countries. The low rate of disseminated *M. avium* in these settings is probably best explained by a high rate of mycobacterial immunity conferred by cross-protection from prior TB and or BCG immunization (von Reyn *et al.* 2002).

Epidemiological studies of disseminated MAC in AIDS have consistently identified several other risk factors for disease including prior *Pneumocystis carinii* pneumonia, exposure to uncooked seafood and prior endoscopy (von Reyn *et al.* 1996, 2002; Ristola *et al.* 1999). Showering has been identified as protective in two different studies, but this finding remains unexplained (Horsburgh *et al.* 1994; von Reyn *et al.* 2002). Molecular epidemiological studies have implicated recirculating hospital hot water systems as the source of two clusters of cases (von Reyn *et al.* 1994).

Detailed water exposure studies have failed to identify the dominant source of exposure to MAC in HIV infection. A study from Los Angeles identified *M. avium* isolates from hospital water that were identical to sputum isolates from non-AIDS patients, but failed to identify water isolates identical to isolates from AIDS patients (Aronson *et al.* 1999). In a recent study of 359 AIDS patients in the United States and Finland, patient-directed potable water samples were cultured for MAC. Overall, 13% of samples were positive for *M. avium*, principally from home water supplies (von Reyn *et al.* 2002). Recirculating hot water supplies had the highest risk of colonization (Arbeit, unpublished) but there was no association between *M. avium* colonization of a patient's home water supply and the risk of disseminated MAC. Only 1 of 31 patients who

developed disseminated MAC was infected with a strain also present in their home water source (toilet bowl water) (von Reyn *et al.* 2002).

Studies have also explored the possible role of other environmental sources. *M. avium* was isolated from potting soil in the homes of AIDS patients in California but typing methods were only able to show that they were similar but not identical to corresponding clinical isolates (Yajko *et al.* 1995). In an investigation of food products from the homes of AIDS patients 1 of 121 food samples was found to have a PCR pattern identical to a clinical isolate (Yoder *et al.* 1999).

Collectively, these findings have been interpreted to indicate that the sources of disseminated MAC in AIDS are diverse and probably not wholly identifiable or avoidable.

7.1.4 Burden of disease

MAC disease is not reportable in the United States but passive surveillance data on disseminated MAC are available for patients with AIDS. Prior to the advent of effective prophylaxis against disseminated MAC in 1993, cases of disseminated MAC were continuing to increase and outnumbered annual cases of TB in the United States. The peak incidence of MAC in the United States was thought to have occurred in 1994 when it was estimated that there were approximately 37 000 people with disseminated MAC (Horsburgh *et al.* 2001). Cases of disseminated MAC are now much less common and occur principally among people with advanced AIDS who are not under medical care or are non-compliant with HAART or MAC prophylaxis (Kovacs & Masur 2000).

7.1.5 Prevention and treatment

In the pre-HAART era disseminated *M. avium* infection was associated with a mean four to five month reduction in survival (Horsburgh *et al.* 1991; Chin *et al.* 1994). Treatment of disseminated *M. avium* with clarithromycin (or azithromycin) and ethambutol increases the survival time of patients. Treatment must be continued indefinitely in patients with advanced AIDS but may be safely discontinued after 12 months in those who are also treated with HAART and experience immune reconstitution (defined as an increase in CD4 count to $> 100/\text{mm}^3$ for at least six months) (Aberg *et al.* 1998; CDC 2002).

Disseminated *M. avium* can be prevented in AIDS patients with CD4 counts $< 50/\text{mm}^3$ by the administration of antibiotic prophylaxis with clarithromycin or azithromycin (Havlir *et al.* 1996; Benson *et al.* 2000). Treatment of AIDS with HAART also eliminates the risk of disseminated MAC in most patients. Thus patients who have been treated with HAART and have an increase in CD4 count to above $100/\text{mm}^3$ for more than three months may be safely taken off antibiotic prophylaxis for MAC (CDC 2002).

7.2 CERVICAL ADENITIS

7.2.1 Clinical aspects

The link between NTM and cervical lymphadenitis was first described by Prissick in 1957 (Prissick *et al.* 1957) when these organisms were isolated from cases of scrofulosis. The first NTM species isolated was named after this lesion: *Mycobacterium scrofulaceum*. Today more than 100 mycobacterial species have been described. Clinical classification separates them into three groups according to their potential to cause diseases in humans: pathogenic; facultative pathogenic; and non-pathogenic species. The most common presentation is cervical adenitis, from which MAC is currently the most frequently isolated agent. Table 7.1 lists the NTM species most frequently encountered in mycobacterial lymphadenitis.

Table 7.1 Selected species of *Mycobacterium* isolated from cervical adenitis in children with normal immunity (in alphabetical order)

Slow growing species	Rapidly growing species
<i>Mycobacterium avium</i> complex	<i>Mycobacterium abscessus</i>
<i>Mycobacterium kansasii</i>	<i>Mycobacterium chelonae</i>
<i>Mycobacterium malmoense</i>	<i>Mycobacterium fortuitum</i>
<i>Mycobacterium scrofulaceum</i>	<i>Mycobacterium xenopi</i>

MAC cervical adenitis usually presents as a unilateral, solid, swelling high in the neck that in most cases is not painful to the touch. The overlying skin might show a purplish discoloration and sometimes a fistula has formed. This swelling is present over a longer period of time (weeks to months) and unresponsive to antibiotic treatment (Wolinsky 1995). Ultrasound examination usually shows no necrosis and small calcifications might suggest mycobacterial disease. In immune-competent children the disease remains localized, the child appears well and further studies including chest x-ray and blood chemistry are unremarkable.

The most important issue for diagnosis is the differentiation of TB and non-tuberculous disease. In MAC adenitis there is no history of exposure to TB. Skin testing for TB usually shows positive results, even strongly positive reactions in some cases, but might also be variable (Chesney 2002). Thus PPD skin testing does not differentiate between tuberculous disease and MAC cervical adenitis. Also, histopathological changes in immune-competent children do not differ significantly. In addition, mixed infections caused by *M. tuberculosis* and NTM have been described.

Acid-fast staining is not species specific and has a low sensitivity. The gold standard for diagnosis of mycobacterial disease is the isolation of the pathogen by culture. Modern

culture techniques have increased the sensitivity of culture isolation of NTM to about 50%. In addition, the time for a positive culture could be decreased to an average of two to three weeks. Nucleic acid amplification tests to detect MAC and other mycobacterial pathogens directly from the specimen are available. They should only be used as an addition to conventional culture, as they exhibit a lower sensitivity. Susceptibility testing of the isolated mycobacterium is not standardized and – with the possible exception of susceptibility to the newer macrolides (clarithromycin, azithromycin) – does not contribute much to the therapeutic decision (American Thoracic Society Statement 1997).

7.2.2 Epidemiology and risk factors

The epidemiological information on mycobacterial cervical adenitis in immunocompetent children is based on a number of case series performed over different periods of time in different geographical regions. A hallmark review by Wolinsky - and its follow-up publication 16 years later - found this disease mostly among young children below five years of age. Girls were more often affected than boys. The initial manifestation started more often in the winter months, sometimes preceded by an upper respiratory tract infection (Wolinsky 1979, 1995). Other studies also showed an intriguing age distribution of mycobacterial adenitis: while in infants and small children the majority of cases are caused by MAC or other NTM, children older than 10-12 years of age and young adults usually suffer from tuberculous lesions.

There are characteristic differences in the geographical distribution of the species. While MAC is the most common pathogen found in cervical adenitis on a worldwide scale, *M. malmoense* is the second most frequently isolated organism in Europe. In the United States however, *M. scrofulaceum* is second and *M. malmoense* is rarely isolated (Benjamin 1987; Clark *et al.* 1994; Grange *et al.* 1995; Wolinsky 1995; Suskind *et al.* 1997).

In western countries with a low incidence of TB (below 20 per 100 000 population) most studies demonstrate a ratio of non-tuberculous to tuberculous mycobacterial adenitis of 4:1 (Wallace *et al.* 1990; Inderlied 1993; Chesney 2002). However, in other countries scrofula is still caused almost exclusively by TB. It has also been suggested that there might be a negative correlation with BCG vaccination in infancy. This suggestion is supported by the efficacy of BCG in prevention of leprosy.

The maturation of the cellular immune response seems to be responsible for the age distribution in non-tuberculous disease. However, it remains unclear why only a small number of children develop clinical disease even though the organisms are ubiquitous in the environment. The genetic analysis of the syndrome of “mendelian susceptibility to mycobacterial disease”, first described by Casanova *et al.* has elucidated some of the underlying specific pathways predisposing to mycobacterial disease (IL-12, INF γ) (Altare *et al.* 1998; Casanova *et al.*, 1999). Other deficiencies in cellular immune defence

such as HIV/AIDS also predispose to disease progression and generalized disease. In addition, iatrogenic immune suppression and – in pulmonary disease – morphological and pathophysiological factors might trigger disease.

7.2.3 Morbidity/mortality

Diseases caused by NTM are not routinely reported in most countries. An exception is Sweden, where incidence data have been published for birth cohorts between 1969 and 1990. During this time an increase in the incidence rate from 1 to 5.7 per 100 000 children younger than 5 years of age was reported (Romanus *et al.* 1995). A similar trend has been reported from clinical observations and laboratory data for other countries, where incidence data are not available (Kuth *et al.* 1995).

7.2.4 Burden of disease

As there is little information about the morbidity caused by mycobacterial adenitis; for most countries, the burden of disease can only be speculated. Even though, mycobacterial adenitis is a rare disease, it seems to be increasing in western countries. This might even happen more rapidly in countries that have stopped BCG vaccination because of the low incidence of TB (Romanus *et al.* 1995). Furthermore, the long-term effect of mycobacterial adenitis and other non-tuberculous disease remains to be studied. One current hypothesis suggests that infection with NTM disease in childhood might play a role in triggering diseases such as CD (Hermon-Taylor *et al.* 1998; see also Chapter 6).

7.2.5 Prevention and treatment

As NTM are ubiquitous, prevention of exposure seems to be difficult, if not impossible, to achieve. For the development of strategies for prevention more surveillance data are needed to estimate the impact of other factors such as BCG vaccination or regional differences on the long-term trend.

As MAC and other NTM species are resistant to antituberculous drugs and most antibiotics, the treatment of choice in localized disease still consists of complete excision of the diseased lymph nodes (Schaad *et al.* 1979; Starke *et al.* 1995). However, depending on the relationship to other anatomical structures, especially the mandibular branches of the facial nerve, surgical intervention carries the risk of transitory or permanent damage to these structures. If the affected nodes cannot be surgically removed or are (inadvertently) drained during the process, local reactivation is likely to occur. In a number of cases, total excision is not feasible and therefore a combined approach including antimycobacterial chemotherapy is used. Usually a triple therapy consisting of a new generation macrolide, a rifamycin derivative, and ethambutol is prescribed for a

period of more than six months. However, there are no large blind randomized trials about the best treatment regimen.

In generalized and reactivated disease the initial treatment approach consists of combination chemotherapy. If surgical revision is indicated — for example because of fistula formation — the procedure requires a very experienced surgeon.

7.3 TENOSYNOVITIS

Soft tissue infections with MAC in immunocompetent patients are rare, but a number of cases of tenosynovitis have been reported, usually following local surgery, trauma or corticosteroid administration (Hellinger *et al.* 1995; see also Chapter 8).

7.4 OSTEOMYELITIS AND SEPTIC ARTHRITIS

Multifocal osteomyelitis caused by MAC has been identified in three patients with a genetic defect of the interferon-gamma receptor and a family history of infections with NTM (Arend *et al.* 2001). Patients had a delayed diagnosis and a protracted illness that responded slowly to multi-drug treatment. In one patient, additional treatment with IFN-gamma was necessary. Macrophages from patients had a reduced responsiveness to IFN-gamma and were heterozygous for a dominant negative mutation in the gene encoding the IFN-gamma binding receptor-1 chain. The infections were limited to skin, bone and lymph nodes. Recurrent MAC osteomyelitis has been associated with a deletion at the 818 residue of the interferon-gamma receptor (Vilella *et al.* 2001). Osteomyelitis and septic arthritis can occur in apparently immunocompetent children (Frosch *et al.*, 2000) and adults (Jones *et al.* 1995; Mahan & Jolles 1995; Pombo *et al.* 1998; Weiner *et al.* 1998; Weigl & Haas 2000; Bridges & McGarry 2002). A case of MAC spinal epidural abscess without vertebral osteomyelitis has been reported in a patient with AIDS (Rotstein & Stuckey 1999). Primary septic arthritis and osteomyelitis can occur in AIDS patients (Blumenthal *et al.* 1990; Sheppard & Sullam 1997). Osteomyelitis caused by MAC may be recurrent (Mahan & Jolles 1995; Kourtis *et al.* 1996) and occasionally disseminated (Bender & Yunis 1980; Collert *et al.* 1983; Zammarchi *et al.* 1987; Kwong *et al.* 1991).

Osteomyelitis can follow trauma (Walz & Crosby 1995), surgery, steroid therapy (Pirofsky *et al.* 1993) and sarcoidosis (Sato *et al.* 1992) and is more common in old age (Tanaka *et al.* 1993).

In disseminated MAC infection the organism may be recovered from bone marrow samples (Ohse *et al.* 1997). Although this can lead to osteomyelitis, this does not appear to result from such colonization in most cases.

7.5 MENINGITIS

MAC infections rarely involve the central nervous system, even in patients with widely disseminated disease (Jacob *et al.* 1993; Gyure *et al.* 1995). On the rare occasions when the central nervous system is involved, MAC is the most common NTM cause of meningitis and has a high mortality rate (Jacob *et al.* 1993; Gyure *et al.* 1995; Weiss *et al.* 1995; Flor *et al.* 1996).

7.6 PANCREATIC INFECTION

Pancreatic infection with MAC is rare but can occur in children with HIV infection (Horsburgh *et al.* 1994; Kahn *et al.* 1995).

7.7 SARCOIDOSIS

Mycobacteria, including MTB, MAC and MAP have been implicated in the development of sarcoidosis. Molecular methods to demonstrate mycobacterial nucleic acid in tissues from patients with sarcoidosis have had mixed results (Ikonomopoulos *et al.* 1999; Li *et al.* 1999; Eishi *et al.* 2002), although *M. avium* and MTB sequences have been found in such tissues (Li *et al.* 1999).

7.8 KEY RESEARCH ISSUES

Cases of disseminated *M. avium* in AIDS have become sufficiently unusual that further epidemiologic studies in this population are not likely to be fruitful. Epidemiologic studies have not been conducted to identify possible sources of disseminated *M. avium* infection among HIV-negative patients with defects in cellular immunity. These cases are also rare but epidemiologic studies might explore possible nosocomial transmission from potable water. Nosocomial transmission of *M. avium* has occurred among AIDS patients (von Reyn *et al.* 1994) and nosocomial transmission of other NTM has also been confirmed using molecular methods among various other patient groups (Phillips & von Reyn 2001). Thus molecular epidemiologic studies of disseminated *M. avium* in HIV-negative populations might focus on hospital water supplies and procedures with demonstrated potential for nosocomial transmission of NTM.

Further work on the epidemiology of lymphadenitis is needed to improve our understanding of the routes of transmission and to aid the design of preventative measures.