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Infections Caused by Opportunistic Mycobacteria: A Review*

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Introduction

The two classical mycobacterial diseases of man are tuberculosis and leprosy but their causative agents, *Mycobacterium tuberculosis* and *M. leprae,* are only two of about 40 species that are included in this genus[1]. The majority of these species live freely in the environment, particularly in watery situations such as swamps, rivers, estuaries and piped water supplies[2]. Occasionally, however, some of these environmental species cause serious, even fatal, disease in animals and man.

In the early part of this century, when tuberculosis was rife in the western world, these opportunist mycobacteria received scant attention and were given dismissive epithets such as 'atypical', 'pseudotubercle' and 'tuberculoid' bacilli. Also, as their classification was in chaos, they were dubbed 'anonymous' mycobacteria. Interest in their role as pathogens of man commenced in earnest in the 1950s with the description of two distinct diseases, namely swimming pool granuloma[3] and Buruli ulcer[4] caused by *M. marinum* and *M. ulcerans* respectively: and also the demonstration of their aetiological role in tuberculosis-like pulmonary disease[5].

Pathogenic mycobacteria

Mycobacteria are divisible into two main groups: the slowly growing and rapidly growing species. From the clinical point of view they are divisible into three groups: the two major pathogens *M. tuberculosis* (including *M. bovis* and *M. africanum*) and *M. leprae*; the environmental species that have been definitely shown to cause human disease, and those that rarely, if ever, do so. Members of the second group are listed in Table 1. Most are slowly growing species: with rare exceptions the only rapidly growing pathogenic species are *M. chelonei* and *M. fortuitum.*

The slowly growing species most frequently encountered in clinical practice are *M. avium, M. intracellulare, M. kansasii* and *M. xenopi.* The former two species are very closely related and are thus usually included together as *M. avium-intracellulare,* while in the USA they are sometimes grouped together with *M. scrofulaceum* as the MAIS complex. Very occasionally, species other than those listed in Table 1 cause disease but usually clinical isolates are unimportant. These include *M. gordonae* and *M. nonchromogenicum.* (The characteristics of the species of pathogenic mycobacteria have been reviewed elsewhere[6].)

Types of disease

There are four main types of disease caused by opportunist mycobacteria: (1) local lesions following traumatic inoculation of acid-fact bacilli into the skin or deeper tissues; (2) localized lymph node involvement;

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(3) pulmonary infections resembling tuberculosis; and (4) disseminated disease.

Warty skin lesions may follow the inoculation of opportunist mycobacteria into superficial abrasions. Such infections are usually caused by *M. marinum* and occur in users of swimming pools and keepers of tropical fish, hence the names 'swimming pool granuloma', 'fish tank granuloma' and 'fish fancier's finger'[7]. Occasionally other species such as *M. kansasii* and *M. chelonei* cause similar lesions.

Mycobacterium ulcerans infection leads to necrosis of subdermal tissue and secondary skin ulceration. This disease occurs in certain 'hot spots' in the tropics and Australia and is thought to follow the introduction of the bacillus into the skin by spiky vegetation.

Post-injection mycobacterial abscesses are usually due to the rapidly growing species *M. chelonei* and *M. fortuitum*. These may occur sporadically in, for example, diabetics[8], or in 'epidemics' when several individuals are injected with material from a contaminated batch of vaccine or drug[9]. Similar infections, also caused by rapid growers, have followed penetrating injuries and surgery. Serious outbreaks of sternal infections have followed open heart surgery[10]. A number of cases of corneal infection by rapid-growing species have also occurred[11], presumably as a result of direct implantation.

Mycobacterium haemophilum is a rare cause of nodular or ulcerative skin lesions and all reported infections have occurred in immunosuppressed individuals, particularly recipients of renal transplants[7,12].

Lymphadenopathy due to opportunist mycobacteria is usually cervical, unilateral and self-limiting. Most cases occur in children under the age of five years[13]. In the adult, the infection may be of this limited form or it may occur as part of a disseminated infection.

As in the case of tuberculosis itself, the lung is the organ most frequently involved in opportunist mycobacterial infection. In many cases there is a predisposing factor such as dust-associated disease, chronic bronchitis, residual cavities from past tuberculosis, carcinoma of the lung, cystic fibrosis, AIDS and other immunosuppressive conditions and autoimmune disease. Occasionally, though, infections occur in the apparently healthy subject. Most pulmonary disease is due to *M. avium-intracellulare, M. kansasii* and, in certain regions, *M. xenopi*; less frequent causes include *M. scrofulaceum, M. chelonei, M. szulgai* and *M. malmoense*, although there has recently been a significant yet unexplained increase in the incidence of the latter in Great Britain[14].

TABLE 1. *Opportunist mycobacteria that cause disease in man.*

Disease usually limited to the skin:		
M. marinum	Swimming pool, or fish tank, granuloma	
M. ulcerans	Buruli ulcer	
M. haemophilum		
Nonspecific tuberculosis-like lesions:		
M. avium ●	*M. xenopi*	*M. chelonei* ■
M. intracellulare ●	*M. malmoense*	*M. fortuilum* ■
M. scrofulaceum ●	*M. szulgai*	
M. kansasii	*M. simiae*	

● The MAIS organisms.
■ Rapidly growing species.

The forms of non-pulmonary disease are similar to those caused by *M. tuberculosis*. Thus single or multiple lesions may occur in bone, urinary tract, central nervous system, lymph nodes, skin and, less frequently, virtually any other system or organ. In other cases, the infection resembles cryptic disseminated tuberculosis with multi-organ involvement. In such cases there is little or no histological evidence of an immune response; indeed, the bone marrow may be teeming with acid-fast bacilli while appearing normal when stained with the usual haematological stains[15]. Such disseminated disease usually occurs in association with congenital or acquired immunodeficiency affecting cell-mediated immunity, including therapeutic immunosuppression following transplant surgery[16] and AIDS[17]. Most cases of disseminated disease are due to *M. avium-intracellulare* or *M. chelonei*.

Epidemiology

The epidemiology of infection due to opportunist mycobacteria differs from that of

TABLE 2. *Eight-year survey (1977–1984) of cultures received and new cases registered at the PHLS Regional Centre for Tuberculosis Bacteriology, Dulwich.*

Period	Total cultures received				New cases of diseases due to			
	Tubercle bacilli ●	Other species	Total cultures	% Other of total	Tubercle bacilli ●	Other species	Total new cases	% Other of total
1977–1978	4458	588	5046	11.7	3538	78	3616	2.2
1979–1980	4530	779	5309	14.7	3584	118	3702	3.2
1981–1982	4079	970	5049	19.2	3316	161	3477	4.6
1983–1984	3708	1115	4823	23.1	2974	176	3150	5.6

● Including *M. bovis* and *M. africanum.*

tuberculosis in several important respects. Tuberculosis is almost transmitted directly from one individual to another, so that the infection rate in a community bears a direct relation to the number of infectious or open cases. Disease due to opportunist mycobacteria is rarely, if ever, transmitted in this manner; almost all cases follow acquisition of the bacilli from their natural inanimate environment. Accordingly, the prevalence of such infections in a community is independent of that of tuberculosis and is unaffected by public health measures designed to reduce the transmissibility of the latter.

As a consequence, the incidence of opportunist mycobacterial infections increases relative to that of tuberculosis in regions where the latter disease is in decline. In addition, the absolute number of cases that are diagnosed annually appears to be on the increase. Table 2 summarizes the experience of the Public Health Laboratory Service Regional Centre for Tuberculosis Bacteriology at Dulwich—a centre that receives over 95% of mycobacteria isolated by laboratories in London and south-east England. Over the last eight years the number of cultures received has remained fairly constant, but while the number of cases of tuberculosis and cultures of *M. tuberculosis* have shown a slight decline, the number of cultures of other mycobacteria and new cases of clinically confirmed disease caused by them have shown an increase which, on time series analysis, is highly significant ($P<0.001$).

The number of cases of opportunist mycobacterial infections in a given area depends on the number of potentially pathogenic strains in the environment, the opportunities that they have for contact with the human population and the susceptibility of the potential hosts. The relative frequency of infections is determined by the distribution of the various species in the environment. Thus the predominant species in the USA and Great Britain are *M. avium-intracellulare* and *M. kansasii* respectively, although *M. xenopi* is the most frequent cause of disease in South East England. The records of the Regional Centre for Tuberculosis Bacteriology, Dulwich, show that of 533 clinically confirmed new cases of opportunist mycobacterial infection, 37% were due to *M. xenopi,* 28% to *M. kansasii,* 20% to *M. avium-intracellulare* or *M. scrofulaceum* and 8% to the rapid growers *M. fortuitum* and *M. chelonei.*

In some cases the source of infection may be obvious, such as the use of a contaminated batch of vaccine[9] or the presence of *M. chelonei* in the piping of a renal dialysis machine[18]. The source of lymph node infection of childhood is not so obvious, but bacilli in food, water and on the multitude of objects that young children insert in their mouths may enter through the tonsil. Pulmonary disease may follow aspiration of ingested bacilli from the pharynx, but there is also evidence that aerosols generated by showers and taps may lead to direct infection by inhalation[2].

Diagnosis

Mycobacterium tuberculosis is an obligate pathogen, thus its isolation from a clinical specimen is a clear indication that the patient has tuberculosis. This is not the case with the opportunist mycobacteria.

As indicated above, mycobacteria abound in the environment and colonize water pipes and taps: they even occur in taps of distilled water supplies and in de-ionizer resins. Great care must therefore be taken in the collec-

tion of specimens and in their bacteriological examination. Apparent outbreaks of opportunist mycobacterial pulmonary disease in hospitals have been traced to the practice of rinsing sputum pots under taps contaminated with mycobacteria[2]. Furthermore, the use of contaminated laboratory reagents has, on more than one occasion, resulted in 'false' reports of small numbers of acid-fast bacilli in stained sputum smears, especially when the smears are prepared from digested sputum concentrates rather than from the original specimen[2,19].

The diagnosis of opportunist mycobacterial disease is made bacteriologically: only cultural procedures can unequivocally determine the species responsible. Immunological tests such as differential skin testing or detection of specific antibodies may help to confirm the diagnosis in some cases, although experience with such tests is rather limited. Once a culture is obtained, a decision as to its clinical relevance must be made. Isolation of a mycobacterium from a biopsy, together with histological evidence of granulomatous disease, usually poses no interpretational problem. Most specimens, however, are sputum and although an isolate may indicate disease it may also indicate transient contamination of the mouth or pharynx or a benign colonization of damaged portions of the respiratory tract. Thus, unless invasive techniques are used, diagnosis usually rests on repeated isolations over several weeks, a high clinical suspicion of active disease and the thorough exclusion of other causes of the signs and symptoms, including tuberculosis[20].

Even greater care must be taken in bacteriological examination of the urinary tract as the urethra and external genitalia are frequently contaminated with acid-fast bacilli though, contrary to a popular myth, *M. smegmatis* is rarely found.

Therapy

The choice of therapy will depend on the site and nature of the infection, the species of causative organism and the presence of any underlying predisposing condition. Lymphadenopathy in young children and localized post-injection abscesses are usually self-limiting, although surgical excision or drainage hastens the recovery. Surgical excision of a localized pulmonary lesion, though now rarely advocated in tuberculosis, should receive serious consideration when the cause is an opportunist mycobacterium[21].

In most deep or systemic infections, antimicrobial therapy is indicated. The *in vitro* susceptibility to drugs varies considerably both between and within the species of mycobacteria. In general, however, drug sensitivity tests have not proved helpful: combinations of drugs to which the bacilli are resistant *in vitro* often prove effective *in vivo*. Therapy is therefore usually empirical and often based on anecdotal evidence or retrospective surveys.

Many therapeutic regimens are based on the antituberculous drugs. *Mycobacterium kansasii* and *M. xenopi* are usually sensitive to a combination of isoniazid, rifampicin and ethambutol—the drugs used in standard modern therapy of tuberculosis. This regimen is often effective against both species, provided that all three drugs are given for 18–24 months[22,23]. Similar therapy has been used successfully for the treatment of *M. malmoense* infections[24]. It has, however, been suggested that shorter, i.e. 12-month, therapy may be effective in *M. kansasii* infections[25]. Although strains of *M. avium-intracellulare* are usually resistant to these drugs *in vitro*, standard antituberculous therapy is often effective provided that there are no complicating factors and the triple therapy is extended for 18–24 months[26]. Such three-drug therapy is replacing previous ones based on five or six antituberculous drugs, although some physicians use the latter for serious or complicated infections[17].

In recent years there has been an increasing tendency to use drugs not normally used in antituberculous therapy. These include erythromycin, amikacin, doxycycline and sulphamethoxazole alone or in combination with trimethoprim. Erythromycin has been used successfully with gentamicin (with which it may show synergy) in the treatment of disseminated *M. chelonei* infection in an immunosuppressed patient[18]. There is also evidence that it is very effective in infections due to *M. kansasii* and *M. scrofulaceum* and in about half of infections due to *M. avium-intracellulare*[27]. Sulphamethoxazole with trimethoprim (co-trimoxazole) appears to be useful, though on somewhat an-

ecdotal evidence, in infections due to several species including *M. chelonei, M. marinum, M. xenopi* and *M. avium-intracellulare*[28].

The antileprosy drug clofazimine is concentrated in the epithelium, bone marrow and reticuloendothelial system and, probably for this reason, is much more effective in disseminated *M. avium-intracellulare* infections than in pulmonary disease. Regimens containing clofazimine and ansamycin (spiro-piperidyl rifamycin) have been recommended for the therapy of such disseminated infections in AIDS victims[17]. In addition, the cephalosporins cefoxitin and ceftizoxime and some newer agents, not yet generally available, have also shown promise in limited investigations. The latter include ciprofloxacin[29] and fludalanine (3-fluoro-2-deutero-D-alanine) in combination with cycloserine[30].

Conclusions

Disease due to the opportunist mycobacteria, though uncommon, provides a serious diagnostic and therapeutic challenge. At the present time, no universal guidelines for diagnosis or therapy can be laid down: each case poses its own particular problems. Accordingly, it is very important that the management of such infections is conducted in close cooperation with a mycobacteriology reference service such as that provided in Great Britain by the Public Health Laboratory Service.

In Great Britain and other western countries the incidence of such disease is increasing relative to tuberculosis and almost certainly also in absolute terms. It is now realized that such opportunist infections are a real threat to those with chronic pulmonary disease and any form of congenital or acquired immunosuppression including AIDS. As it is impossible to isolate man from the mycobacteria in his environment, it is evident that such infections will remain with us when, hopefully, tuberculosis will have become an historical curiosity.

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