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Skin, bone and soft tissue infections

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This chapter describes the multiple environmental mycobacteria species that can cause skin, bone and soft tissue infections. The etiologic organisms, environmental exposures and clinical presentations will be highlighted.

Infection can occur after traumatic inoculation, as part of a disseminated infection, or from a medical or cosmetic procedure. Risk factors include certain hobbies and occupations as well as various forms of immunosuppression. The source of exposure for skin and soft tissue infection by PEM is usually water or soil: person-to-person transmission has not been demonstrated.

An important cause of skin and soft tissue infection is the agent responsible for BU. BU is the third major mycobacterial disease of man after TB and leprosy. The name derives from a region in Uganda where the disease was common in the 1960s and 1970s (Barker 1972). The responsible bacterium, *Mycobacterium ulcerans,* produces a toxin called mycolactone that causes necrosis of skin and subcutaneous fat and has immunosuppressive properties (George *et al.* 1999). Sufferers of BU are generally healthy individuals with no known underlying immune defect.

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Additional details regarding skin infections can be found in the chapter dealing with invasive devices and procedure (Chapter 10). For the interested reader, an excellent review on NTM infections of the skin has recently been published (Weitzul *et al.* 2000).

8.1 CLINICAL ASPECTS

PEM can cause a variety of skin and skin structure infections. The clinical presentation can be quite variable. Most patients are relatively healthy and acquire disease from minor trauma with exposure to the environment (soil or water). Lesions tend to be fairly indolent, but severe disease can occur. The initial exposure can be hard to track as the incubation period can be quite long. Disseminated disease should alert the clinician to an immunocompromising condition such as malignancy, medications used to suppress the immune system, HIV or defects in cytokine pathways (IL-12 and gamma-interferon). Some of the organisms involved require special knowledge of optimal cultivation methods in the laboratory. Examples of a few of the major species and the nature of the disease they cause are described below.

8.1.1 *M. marinum*

M. marinum skin infections have been observed in people who own aquaria, people who work with water, and those who use water for recreational purposes (Huminer *et al.* 1986). It has been associated with both salt and fresh water exposures. Certain occupations such as aquatic farming represent a high-risk group. Also, farmers and nursery garden workers appear to be at greater risk.

Several studies of disease caused by *M. marinum* have been reported. In Australia, 29 patients were reported with *M. marinum* infection following trauma and exposure to an aquatic or timber source (Iredell *et al.* 1992). In a study from Chesapeake Bay, USA, Hoyt *et al.* (1989) reported infection predominantly in males and that cutaneous infection was most common. In contrast, Edelstein (1994) found that in northern California over 50% of the victims with skin infections due to *M. marinum* were female. The major risk factor for infection was contact with fish tanks. A large outbreak of *B. balnei* (later identified as *M. marinum*) infection was identified in an open-air hot springs pool (Collins *et al.* 1985). In this outbreak, and others like it, skin lesions were predominantly located on the elbows and less often the knee, foot, finger and toes. Skin lesions were often superficial and verrucal. Acid-fast stain is often negative in biopsy and drainage samples. Lymphadenopathy is unusual but does occur (Huminer *et al.* 1986). Most lesions healed spontaneously. A positive skin test to tuberculin has been reported even long after the lesions healed (Judson & Feldman 1974).

There is often a delay between the development of symptoms and proper diagnosis of sporadic cases. The lesions of these infections can be variable in presentation but they often begin as a reddish violaceous nodule that goes on to ulcerate. A common presentation is nodular lymphangitis (or sporotrichoid spread) consisting of subcutaneous nodules with satellite lesions that can ascend up the extremity by lymphangitic spread (Wolinsky *et al.* 1972). While the finding of sporotrichoid disease can be seen in other infectious (including mycobacterial diseases), it has been particularly well described with *M. marinum*. The most frequent location is the right middle finger. Disease is most often limited to the skin but can cause adjacent joint and tendon infections. In addition to nodules, cutaneous lesions include pustules, verrucous lesions, red plaques, abscesses, seromas and ulcers. Synovitis and arthritis are seen rarely. Dissemination can occur in the immunocompromised host (Gombert *et al.* 1981; King *et al.* 1983; Enzenauer *et al.* 1990; Tchornobay *et al.* 1992; Parent *et al.* 1995; Holmes *et al.* 1999; Enzensberger *et al.* 2002). Pathologic specimens reveal granulomas which can be non-caseating; there can be suppurative inflammation, micro-abscesses and necrosis. The immunocompromised patient may have less well-formed granulomas.

Often acid-fast staining of tissue or drainage is negative and the diagnosis is made by culture. The organism has a growth temperature optimum of 30-32 °C, Diagnosis is usually suggested on clinical grounds, but identification of the organism in the laboratory is crucial. Clinicians should inform the laboratory of the suspicion of the organisms so that the laboratory can set up the material for mycobacterial culture at lower temperature in addition to routine cultivation procedures. Susceptibility tests can be performed once the isolate has been grown. Lesions in the immunocompetent host can resolve spontaneously; however, most experts would begin combination antimicrobial therapy when a diagnosis is made. Agents that have been used include rifampin, ethambutol, trimethoprim/sulfamethoxazole, clarithromycin, fluoroquinolones and doxycycline/minocycline. Success has been reported with trimethoprim/ sulfamethoxazole alone. Consultation with an experienced surgeon may be indicated for the removal of infected and devitalized tissues. The optimal duration of therapy is unknown, although three to six months is normally the minimum; many experts recommend a longer course. Tendon and joint infection requires longer periods of therapy with the use of surgical debridement if chemotherapy alone is not successful (Aubry *et al.* 2002). In the hand, surgical treatment is often required to control the infection. Occasionally, heat is applied to the limb in an attempt to inhibit the organism's growth (Sutherland *et al.* 1980).

8.1.2 Rapidly Growing Mycobacteria

Infection of the skin and soft tissues with RGM is not uncommon (Wallace *et al.* 1992). In a recent case control study of *M. fortuitum* furunculosis associated with footbaths in California, the risks for acquiring infection was related to shaving the legs with a razor before pedicure (odds ratio 4.8) (Winthrop *et al.* 2002). Microabrasion with the razor could explain the portal of entry. Cultures of salon tap water yielded other species of RGM (*M. abscessus/chelonae*). Cultures from the footbaths yielded *M. fortuitum*. Some were indistinguishable from the clinical isolates on the basis of PFGE. Some of the infections reported in these individuals were associated with severe scarring furunculosis. This important large community outbreak, and prior reports of rapidly growing mycobacterium skin infections associated with hot tubs and public baths, highlight the important role that waterborne mycobacterial pathogens play in skin infection (Aubuchon *et al.* 1986; Lee *et al.* 2000a). The frequency of isolation of these pathogens and the burgeoning nail salon and cosmetic industry suggests that additional cases may occur.

Injection site abscesses have been reported, most often secondary to *M. abscessus*. Other rapidly growing species such as *M. chelonae, M. smegmatis* and *M. fortuitum* have also been implicated in a variety of similar situations. These have often occurred as the result of iatrogenic exposures, cosmetic procedures and complications related to alternative medicine practices (Wallace *et al.* 1983; Safranek *et al.* 1987; Camargo *et al.* 1996; Murillo *et al.* 2000). *M. abscessus* tenosynovitis has been reported in a health care worker who had a penetrating injury due to a contaminated scalpel (Wolinsky 1992). *M. abscessus* is one of the most common causes of post-surgical mycobacteria infections, especially after plastic surgery. *M. abscessus* and *M. fortuitum* have caused skin infections after iatrogenic procedures such as liposuction, facial blepharoplasty, augmentation mammoplasty and other cosmetic procedures (refer to Chapter 10). A common finding in *M. abscessus* infections of the skin is the formation of violaceous to red tender nodules that can form fistula. Fistula formation can be severe and can track to the surface in multiple sites.

Therapy for RGM infections is generally guided by *in vitro* antimicrobial susceptibility testing. Clarithromycin, cefoxitin and amikacin are among the most effective antimycobacterial agents for *M. abscessus*. Single-drug therapy with clarithromycin has been effective but failures have been reported due to the emergence of drug resistance (Vemulapalli *et al.* 2001). Susceptibility tests for the rapid growing species can also be used to guide therapy to other potentially effective agents such as trimethoprim/sulfamethoxazole and doxycycline, and fluoroquinolones. As with other infections, skilled surgical debridement of necrotic tissues and subsequent wound management is important in the successful outcome of many of these infections.

Other reported cutaneous manifestations of *M. abscessus* include Sweet syndrome and nodular panniculitis (Rotman *et al.* 1993; Choonhakarn *et al.* 1998; Retief & Tharp 1998; Bowenkamp *et al.* 2001). Sweet syndrome presents with fever, elevated white blood cells, erythematous plaque-like skin papules and neutrophils on histopathology. A recent report of disseminated disease due to *M. abscessus* manifest as lymphadenopathy and various organ involvement due to RGM revealed a high incidence of Sweet syndrome (Chetchotisakd *et al.* 2000). These patients were seronegative for HIV. Suspicion of a defect in cell-mediated immunity was raised but not confirmed.

8.1.3 *Mycobacterium avium* complex

Both *M. intracellulare* and *M. avium* have been reported to cause cutaneous, joint, tendon and skeletal disease. Isolated lesions tend to be nodules, which rarely ulcerate. There can also be tenosynovitis, panniculitis, fasciitis, or synovitis. Typically the infections have been localized to soft tissues of the anterior surface of the hand and wrists. Tenosynovitis frequently involves the upper extremity and is a result of inoculation following minor trauma. Incubation times between the event and the presentation to a health care provider can be substantial. The antecedent source is often not clear, and diagnosis can be difficult. Patients are frequently misdiagnosed with arthritis or other inflammatory conditions and have received systemic or local injection of corticosteroids before a proper mycobacteriology diagnosis is made (Hellinger *et al.* 1995; Zenone *et al.* 1999). This can aggravate the disease. The right distal extremity is more often affected. The typical patient is immunocompetent and in the fifth to seventh decades of life. Men and women appear fairly equally affected (Hellinger *et al.* 1995). Symptoms include swelling and violaceous to red discoloration of the overlying skin. The lesions can be tender. Surgical debridement is an important component of diagnosis and therapy. During the operation, the finding of "rice bodies" is felt to be characteristic of mycobacterial infection (Sanger *et al.* 1987). Pathology of tendon infection shows chronic tenosynovitis often with granulomatous inflammation. Other mycobacterial causes of tenosynovitis include *M. kansasii, M. fortuitum, M. terrae, M. chelonae, M. malmoense, M. xenopi* and *M. abscessus* (Zenone *et al.* 1999).

MAC is a rare cause of osteomyelitis and can occur in both immunocompetent and immunocompromised hosts (Chan *et al.* 2001; see also Chapter 7). Localized pain, immobility and, if disseminated disease is present, fever, night sweats and weight loss can occur (Marchevsky *et al.* 1985).

Cutaneous manifestations of MAC infection also include disseminated disease in patients who have defects in immune function including AIDS. Those with severely depressed CD4 cells are most at risk. Since MAC, *M. haemophilum, M. szulgai, M. tuberculosis* and other species have been reported to cause skin manifestations in patients with AIDS, proper microbiological diagnosis is key for management of these patients. Histopathologically, lesions in immunocompromised patients can be atypical (Bartralot *et al.* 2000). While HAART to improve immune function is the cornerstone in management of MAC infection in AIDS, clinicians should be aware that osteoarticular, cutaneous, and other unusual disease presentations can also develop or exacerbate when cellular immunity is restored (Nalaboff *et al.* 2000).

The diagnosis should be clear for all the above infections if careful attention is paid to proper biopsy, histopathology, microbial identification and susceptibility testing. Therapy is complex and multiple drug-drug interactions occur especially for patients taking other medications (such as HIV therapy). Consultation with experts in treating these infections is recommended. Therapy is typically continued for 12-24 months and consists of multiple antibiotics typically including clarithromycin, rifampin and ethambutol. Additional therapy such as an aminoglycoside (i.e. amikacin) is sometimes included for a limited time. In many cases, especially if there is devitalized tissue, surgery can also contribute to curative therapy. In cases of severe tenosynovitis of the wrist or hand, patients require extensive debridement often along the entire length of the tendon sheath. Splinting immediately after the procedure is often done and aggressive hand physical therapy as soon as wound healing allows is often undertaken.

8.1.4 *M. haemophilum*

This organism is a fairly recently recognized pathogen and causes disseminated cutaneous lesions in immunocompromised patients. The lesions often ulcerate. In addition to the skin it can occur in bones, joints, lymphatics and lungs (Straus *et al.* 1994). The cutaneous lesions are violaceous and most often tender. Abscesses with small amounts of serosanquinous drainage have been reported. The cutaneous lesions can be multiple and tend to cluster on the extremities (Dever *et al.* 1992). They also frequently overlie a joint. These findings are consistent with the preference of the organism for lower growth temperatures. In contrast to *M. marinum*, the distribution is typically not sporotrichoid. People at risk are those with defects in cellular immune function such as those with HIV, transplants, lymphoma or those taking medications to suppress immune function. In one study, infection presented a mean of 16 months after an AIDS diagnosis (Straus *et al.* 1994). Pathology shows minor necrosis, poorly formed granulomas and both extracellular and intracellular acid-fast organisms. In the laboratory, *M. haemophilum* is fastidious, requires iron-supplemented growth media, and has a lower temperature for incubation than most other mycobacteria. These facts have likely resulted in a lower historical detection rate. *M. haemophilum* infections have been sporadic and the reservoirs and mode of transmission are not clear.

8.1.5 *M. ulcerans*

BU due to *M. ulcerans* is a great public threat. In certain geographical regions the incidence of BU is increasing. Children are disproportionately affected. Rates in some villages in Africa are greater than 15% (Marston *et al.* 1995). New data has implicated an aquatic insect in the transmission of the disease and this may be the basis for beginning a control programme (Marsollier *et al.* 2002).

BU is painless and slow to develop. A typical Buruli lesion is an extensive, deeply undermined skin ulcer that heals by scarring. There are other presentations including nodules, plaques, oedematous swelling of a whole limb or the abdominal wall and osteomyelitis (Buntine *et al.* 2002). Death due to BU is rare but permanent deformities are common. The diagnosis of BU is likely if large numbers of acid-fast bacilli are present in smears or histological sections obtained from a suspicious lesion. The presence of *M. ulcerans* can be rapidly confirmed by a specific and sensitive PCR (Ross *et al.* 1997; Russell *et al.* 2002). Culture confirmation may take some weeks.

Patients often delay seeking medical assistance until disease is advanced. The main mode of treatment is surgery, with the aim of totally excising early lesions or, in established disease, removing necrotic tissue and grafting the resulting defect. There is current interest in combination antibiotic therapy as an adjunct to surgery, or alone for very early lesions (Etuaful *et al.* in press).

8.1.6 *M. terrae*

This complex of organisms (including *M. terrae, M. trivale* and *M. nonchromogenicum*) is a rare cause of cutaneous infection (Zenone *et al.* 1999; Bartralot *et al.* 2000). Tenosynovitis is the most commonly reported manifestation (Smith *et al.* 2000). Pathological specimens reveal granulomas with multinucleated giant cells.

In common with several other mycobacterial infections, studies of empiric therapy have not been done. Rifampin and ethambutol containing regimens tended to have a better outcome but did not reach statistical significance (Smith *et al.* 2000). Some of the predisposing exposures for skin/tendon infection presented in the literature include farming, fish tanks and gardening, and other soil exposures.

8.2 OVERALL BURDEN OF DISEASE

BU is an important disease because the incidence is increasing, it is expensive to treat, and it is most common in regions that lack advanced medical facilities. For example, a recent study has estimated the cost per case in Ghana at 780 USD (Asiedu 1998). BU has become a major burden for poor agricultural communities in West Africa. In Australia, one of the very few Organisation for Economic Co-operation and

Development countries where transmission of *M. ulcerans* occurs, the cost per case has been conservatively estimated at 12 000 USD (Drummond 1998).

A recent report from Ghana has estimated a national prevalence of 20.7/100 000 in 1999 (Amofah 2002). In one highly endemic region in Ghana an annual incidence of 280/100 000 was reported - higher than TB in the same region (Ragunathan *et al.* 2001). The disease rates in Uganda have been estimated at 2-5% of the population and in Côte d'Ivoire and Ghana; the rates in some villages have been estimated at 16% and 22% respectively (Amofah *et al.* 1993; Marston *et al.* 1995). Disabilities resulting from BU disease are severe and it has been estimated that 25% of cases are left with some disability in Côte d'Ivoire (Marston *et al.* 1995) and 58% in a recent study in Ghana (Ellen *et al.* 2003).

The global burden of BU has not been established but concern about the emergence of BU prompted WHO to create a specific programme for BU in 1998 (GBUI: Global Buruli Ulcer Initiative).

Disease due to PEM is not reportable in the Unites States. Ascertaining the precise incidence and prevalence data is therefore not possible. While some general conclusions can be gleaned by looking at laboratory-based surveys, such surveys have significant limitations. It is difficult to determine how many patients are involved given that the reporting is culture-based, not patient-based, and a single individual may have more than one specimen submitted. However, since 1993 a Public Health Laboratory Information System method of reporting by State Health Departments has proved useful for tabulating data on the environmental mycobacteria. The population under study are those patients in the United States who have had a specimen submitted for evaluation. Only one isolate for each patient was recorded. Compared to historical rates, it appears that the incidence of *M. marinum* and *M. haemophilum* has increased (Bean *et al.* 1992; Dobos *et al.* 1999).

8.3 DISTRIBUTION

Mycobacteria are found in soil and water and often (but not always) the inoculation event can be traced to a specific exposure. In many of the infections due to these organisms transmission occurs via minor trauma to the skin. For *M. marinum* and *M. ulcerans*, water appears to be the major source. For *M. haemophilum*, water has been suggested as a source but the actual reservoir is not completely understood. Patients infected with other species of PEM may have acquired the infection from soil, water or an otherwise unknown source.

While mycobacterial skin disease is believed to be worldwide, certain infections have limited geographic occurrences. BU has been reported in many tropical and some temperate countries, and it is endemic in parts of sub-Saharan Africa. There are also established foci in the Americas, Asia, Australia and Papua New Guinea (Asiedu *et al.* 2000).

8.4 DESCRIPTIVE EPIDEMIOLOGY

Infection is acquired from the environment and person-to-person spread has not been described. Systematic studies of the epidemiology of infections have not been done. For a few of the infections, some general comments can be made.

BU endemic areas are usually near tropical marshes, rivers or lakes but transmission also occurs in temperate southern Australia (Horsburgh 1997). BU is typically unevenly distributed within an endemic country. New areas of micro-endemicity may appear unpredictably (Johnson *et al.* 1996).

Unlike TB and leprosy, BU is contracted by exposure to a contaminated environment rather than from infected people. Most patients with BU are children below the age of 15. A study from Amansie West in Ghana reported the median age as 12 years, with 49% of cases aged 10-14 years. Only 20% were over 50 years old (Amofah *et al.* 1993). Recent reports from Benin suggest that there is also an increased attack rate of BU in the elderly, resulting in an age-specific incidence similar to that observed for TB (F. Portaels, personal communication). The precise mode of transmission has not been established, but recent work has suggested that aquatic insects and biofilms attached to aquatic plants harbour *M. ulcerans* (Marsollier *et al.* 2002). Transmission of *M. ulcerans* from infected insects to laboratory mice has been demonstrated, but whether this is how humans become infected remains unknown. Transmission by aerosol or through direct contact with contaminated soil has also been proposed. It is possible that more than one mode of transmission exists. It has been suggested that environmental changes such as logging, mining and nutrient enrichment of waterways is contributing to the spread of BU.

Recent serological data from Australia has suggested that the rate of household exposure to *M. ulcerans* within endemic areas may be quite high (Gooding *et al.* 2002). It is not understood why some individuals are affected while the majority remain disease free. There is no convincing evidence of an increased incidence of BU in patients with HIV, diabetes or medically induced immunosuppression.

In the majority of reports the mean age of people with *M. marinum* is the fourth to fifth decade of life and Caucasian males are most commonly affected. Trends in rates of infection are largely unknown; however the recorded incidence of *M. haemophilum* may increase as culture methods improve and as clinicians become more aware of the organism.

8.5 RISK FACTORS

Most infections are thought to occur by local inoculation as a result of accidental or unapparent trauma. Local steroid injections can also worsen undiagnosed skin infections that have occurred as a result of trauma. These infections can occur in immunologically normal individuals.

The main risk factor for BU is contact with an endemic region. The period of exposure can be very short, but most affected people are residents of these areas. There is circumstantial evidence that wearing clothing (trousers) may be protective (Marston *et al.* 1995).

Exposure to contaminated solutions or devices is another risk factor for other PEM and iatrogenic infections are dealt with in the invasive procedures chapter (Chapter 10). In severely immunocompromised patients, it is likely that the skin lesions have occurred as a result of haematogenous dissemination rather than direct inoculation. In summary, immunodeficiency, abnormal defensive barriers as a result of skin injury and exposure to certain sources (i.e. soil, water and contaminated solutions or devices) are risk factors associated with infection.

8.6 CAUSALITY AND ASSOCIATED MICROBES

Table 8.1 contains a list of PEM species that have been reported to cause skin infections:

Table 8.1 Classification of PEM species that have been reported to cause skin infections (Based on the criteria of Runyon*)

Class	Species name
Photochromogens	*M. marinum*
	M. kansasii
Scotochromogens	*M. scrofulaceum*
	M. szulgai
Non-photochromogens	*M. avium*
	M. intracellulare
	M. ulcerans
	M. haemophilum
	M. terrae complex
	M. xenopi
Rapidly growing species	*M. abscessus*
	M. chelonae
	M. fortuitum
	M. smegmatis

*Runyon criteria: Rapid growers grow in seven days or less. Scotochromogens produce pigment when grown in the dark as well as upon exposure to light. Photochromogens produce pigment when exposed to light but not when grown in the dark. Nonchromogens do not produce pigment even after light exposure.

8.7 KEY RESEARCH ISSUES

In common with other mycobacterial infections, it will be important to systematically study the epidemiology and causative microbes. To achieve this, standard case definitions and accurate microbial identification should be emphasized. Use of new molecular tools for species identification and for strain typing of clinical and environmental isolates to understand the epidemiology is important. The prognostic value of *in vitro* antibiotic susceptibility tests for clinical outcome needs to be determined for these and other PEM infections. Given the small numbers of cases in single centres, multicentre studies will be necessary. Since therapy is toxic and expensive, determining the proper agents and duration of therapy will be important. Encouraging pharmaceutical companies to develop better antimycobacterial therapy is important. Studies are required into the role of topical therapy and the use of antibiotic-impregnated polymethacrylate beads and cement placed intraoperatively as a means of attaining a higher local concentration of the antibiotic. If newer potent agents were developed it may lessen the need for such long-term courses of therapy. Elucidation of the reservoirs for *M. haemophilum* and other species will be illustrative. Study of the climatic and other environmental changes that may predispose to favourable conditions allowing these emerging pathogens to exist is an important avenue of future research. Additional studies of unique species-specific virulence factors, host tropism, environmental niches and modes of transmission will be a fruitful area of investigation with far-reaching benefits for patients.