Mycobacterial Infections

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1. Introduction

Mycobacteria are aerobic, non-spore-forming, non-motile, bacterial rods. They possess a thick, hydrophobic cell wall that contains high concentrations of lipids and mycolic acids, which makes them resistant to decolorization with acid-alcohol following application of acid-fast stains such as Ziehl-Neelsen and Fite's stains. There is regional variation in the incidence of disease caused by different mycobacterial species. This may result from environmental factors that promote survival of mycobacteria in the environment, differences in host susceptibility relating to host genetics, host behavioral factors such as outdoor roaming, the presence of wildlife and domestic animal reservoirs, and exposure factors such as consumption of raw beef products or interactions with wildlife. Regional differences exist in diagnostic tests that are available and access to laboratories with experience isolating and characterizing mycobacteria. There are also regional differences in mycobacterial drug susceptibility and availability of specific antimycobacterial drugs. Mycobacteria can be divided into three groups described below.

2. *Mycobacterium tuberculosis* complex (MTBC) infections

The primary MTBC organisms that infect cats are *M. bovis* and *M. microti*; most of these infections have been reported from the UK and western Europe.[1] Rodents are reservoir hosts for *M. microti,* although infections have also been recognized in cattle and goats.[2] Cattle and a variety of wildlife species are reservoir hosts for *M. bovis.* The identification of a growing number of wildlife reservoir host species for *M. microti* and *M. bovis* has complicated efforts to eradicate *M. bovis* in different parts of the world.

Infected cats are often young adult male cats with a history of predation; transmission occurs through ingestion of prey or cutaneous inoculation. Transmission to cats has followed ingestion of unpasteurized milk; the feeding of commercial venison raw food diets to cats in the UK also has been associated with infection.[3] There has been no

association with retrovirus infection. Most cats have single or multiple nodular cutaneous lesions. Local lymphadenomegaly is often present. Gastrointestinal involvement may follow infection after ingestion, and respiratory involvement may follow inhalation or dissemination from the skin. Dissemination may also occur to a variety of other sites, such as the bones, liver, spleen, lymph nodes, and eyes.

In dogs, MTBC complex infections are usually caused by *M. tuberculosis* or *M. bovis*; *M. microti* infections are rare.[4] *Mycobacterium tuberculosis* infection in dogs is considered a reverse zoonosis and so is more likely to occur in parts of the world where the incidence of *M. tuberculosis* infection in humans is high. Infections with *M. tuberculosis* and *M. bovis* typically manifest as pulmonary, gastrointestinal, or disseminated disease without skin involvement; skin lesions are rare.

The number of intralesional acid-fast bacilli (AFB) visible in granulomas is variable. Nucleic acid amplification tests are available that detect and differentiate between NTM and MTBC organisms, but they do not distinguish among MTBC species. In the UK, an interferon-gamma release assay has been developed that aids in differentiation between *M. bovis* and *M. microti* infections in cats.[5] Identification of MTBC to the species level requires culture at specialized laboratories followed by a series of biochemical tests, with or without spoligotyping (a PCR-hybridization method). This may take weeks to months.

A combination of a fluoroquinolone, a macrolide/azalide and rifampicin is suggested for treatment of cats and dogs with MTBC infections.[1] Three months is the minimum duration of treatment; treatment should be extended for two months beyond resolution of clinical signs. Disease caused by MTBC bacteria is usually notifiable to public health authorities. However, human disease resulting from exposure to companion animals infected with *M. bovis* is rare (and usually due to exposure to draining skin lesions),[1,6] and no human infections with *M. microti* have been reported because of exposure to infected cats.[7] Pursuing treatment is controversial when there are humans in the household that are immunosuppressed.[1] Owners should be referred to human health professionals for follow-up after exposure to infected dogs and cats.

3. Non-Tuberculous Mycobacterial (NTM) Infections

3.1 Slow-growing NTM Infections

The most common slow-growing NTM causing disease in cats and dogs are organisms that belong to the *Mycobacterium avium* complex (MAC). Other NTM species include *Mycobacterium genavense*, *Mycobacterium malmoense, Mycobacterium kansasii*, and *Mycobacterium ulcerans.*

In cats, disease caused by MAC organisms resembles that caused by *M. bovis* or *M. microti*, including cutaneous lesions and evidence of systemic dissemination. Advanced FIV infection or treatment with immunosuppressive drugs may predispose cats to MAC infection.[1] Certain lines of Abyssinian and Somali cats may also be predisposed.[8] In dogs, MAC infection most often manifests as disseminated disease. Disseminated MAC infections in miniature schnauzers have been associated with a deficiency of CARD9.[9] *Mycobacterium ulcerans* causes localized ulcerative cutaneous lesions in southeastern Australia and Africa.[10] The bacterial toxin *mycolactone* is responsible for deep skin ulcerations.

In general, larger numbers of mycobacteria are identified in smears or biopsies in slow-growing NTM infections when compared with MTBC infections and rapid-growing NTM infections.[1] However, in some MAC infections, AFB are undetectable.[11] Diagnosis can be confirmed using PCR with or without culture. Use of PCR-sequencing allows slow-growing NTM to be identified to the species level. Up to 3 months of incubation may be required for visible growth of MAC organisms in culture, and in some cases, culture may never yield growth.[12] Susceptibility testing using broth microdilution also should be performed by mycobacterial reference laboratories.

As for infection with MTBC organisms, the use of 2 or 3 drugs in combination is recommended to prevent emergence of resistance; various combinations of clarithromycin, clofazimine, doxycycline, rifamycins, and fluoroquinolones have been used in cats and dogs. Mycobacteria that belong to the MAC are often resistant to enrofloxacin and marbofloxacin. Treatment success has been variable; animals with disseminated MAC infections due to irreversible immunosuppression often are ultimately euthanized, but cure has been reported in a few cats and in the dog with localized MAC infection. Treatment for MAC infections is typically required for long periods (months to years), and sometimes it must be continued indefinitely.[1] Lesions in dogs infected with *M. ulcerans* have resolved following treatment with fluoroquinolones, with or without a rifamycin.[10] Humans acquire MAC infections by slow-growing NTM from the environment, often in association with underlying

immunosuppressive illness; direct transmission from diseased dogs and cats to people has not been described.[1]

3.2 Rapid-growing NTM Infections

Rapid-growing NTM (widely referred to as RGM) generally grow in culture within 7 days and are responsible for most cutaneous mycobacterial disease in cats in the USA and Australia. Infections have also been described in the UK, Canada, western Europe, New Zealand, and South America.[1] Rapid-growing NTM that are pathogens in cats include members of the *Mycobacterium fortuitum* group, *Mycobacterium smegmatis* group, *Mycobacterium chelonae/abscessus* group, and *Mycobacterium thermoresistibile*.[1] Rapid-growing NTM infections in dogs are less commonly reported than they are in cats. Infections in dogs that involve the skin have been reported with *Mycobacterium goodii*, *Mycobacterium smegmatis* complex, *M. chelonae* complex, and *M. fortuitum* complex.[1]

Infection with RGM generally follows cutaneous inoculation, such as from penetrating plant wounds or following contamination of surgical wounds. Inoculation of the organism directly into subcutaneous adipose tissue may increase the severity of disease. Affected cats and dogs are typically well and in good body condition. Skin lesions are characterized by multiple punctate draining tracts and subcutaneous nodules. In cats, lesions usually involve the inguinal region. In dogs, lesions are often found on the cervicothoracic region, trunk, or caudal dorsum.[1]

On histopathology, panniculitis lesions are characterized by granulomatous to pyogranulomatous inflammation and often few visible mycobacteria; in addition, rapid-growing NTM are not as acid-fast as other mycobacterial species.[1] Organisms typically grow rapidly on routine media and MALDI-TOF or PCR-sequencing can be used for identification to the species level. However, in some cases, weeks of incubation are required.[13] Submission of deep biopsy for macerated tissue culture may increase the chance of more rapid isolation. Antimicrobial susceptibility testing by experienced laboratories is recommended because of frequent multidrug resistance.[14] Based on typical susceptibility patterns recognized at the time of writing,[1] in areas where *M. smegmatis* and *M. fortuitum* complex infections predominate, treatment should commence empirically with pradofloxacin. Where *M. chelonae* infections are more commonly diagnosed, the best first line choice is clarithromycin or azithromycin. Multi-drug therapy is recommended;

doxycycline would be an appropriate choice for combination therapy. Treatment should continue for at least 1-2 months after lesions have resolved. Rapid-growing NTM are opportunistic, environmental mycobacteria that are not transmitted from animals to humans.

4. Fastidious Mycobacterial Infections

In cats, fastidious mycobacteria such as *Mycobacterium lepraemurium*, *Mycobacterium visibile*, "*Candidatus* Mycobacterium tarwinense," and "*Candidatus* Mycobacterium lepraefelis" cause nodular cutaneous lesions ("feline leprosy syndrome"). Cutaneous inoculation through rodent bites or cat fight wounds is the suspected mode of transmission. "*Candidatus* Mycobacterium lepraefelis" can cause disseminated infections that involve other organs.[15] Disease caused by fastidious mycobacteria in dogs is known as canine leproid granuloma syndrome (CLGS). Most lesions occur in short-coated breeds (especially boxers) and often on the pinnae and head. Lesions are single or multiple firm cutaneous nodules. There is typically no regional lymph node involvement. The syndrome is generally thought to be caused by an uncharacterized fastidious mycobacterium related to slow-growing NTMs.

Cytologic examination of fine needle aspirates from dogs and cats reveals pyogranulomatous inflammation with variable numbers of AFB. Because these organisms often do not grow in culture,[16] direct PCR-sequencing from clinical material is required to determine the likely species present. In cats, treatment typically involves wide surgical resection of skin lesions, plus clarithromycin combined with rifampicin, or pradofloxacin. Disseminated infections caused by "*Candidatus* Mycobacterium lepraefelis" have been associated with poor treatment outcomes.[15] In dogs, most cases of CLGS resolve spontaneously within 1 to 3 months, but persistent lesions should be treated with anti-mycobacterial drug combinations. Wide surgical resection may be curative for localized lesions.

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