Mycobacterioses in Cats: ABCD guidelines on prevention and management

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CLINICAL REVIEW

MYCOBACTERIOSES IN CATS
ABCD guidelines on prevention and management

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Overview: Mycobacterial infections are important in humans and animals. Cats can be infected by several *Mycobacterium* species, which may cause different syndromes, mainly tuberculosis, atypical or non-tuberculous mycobacteriosis and leprosy. In recent years, awareness has increased about how to recognise and confirm these infections. More cases are diagnosed today, which probably means that the disease has escaped detection in the past.

Infection: Most cases in cats are cutaneous, presenting as nodules in the skin and draining tracts, ulceration and local lymphadenopathy; however, systemic dissemination may also occur.

Diagnosis: Definitive diagnosis is difficult when the bacterium cannot be detected by histology or culture. However, species confirmation is essential for treatment and prognosis, so material for culture and polymerase chain reaction should be submitted in every suspected case.

Treatment: Treatment is challenging. A combination of two or three antibiotics is needed, and treatment must be continued for some months, which makes owner compliance especially difficult in cats.

Zoonotic risk: There is a zoonotic risk associated with some mycobacterial species. Concerns should be communicated in every case of an immunocompromised owner in contact with an infected cat.

Bacterial properties

Mycobacteria are intracellular, acid-fast, slow-growing bacilliform bacteria, highly resistant to environmental conditions.[1,2] Mycobacterial taxonomy is complex and many species can infect the cat and induce a variety of clinical presentations. Different classifications have been made in the past based on features and ability to grow in culture, as well as biochemical properties.[2] The use of molecular techniques has led to taxonomic changes, and some species have been or will be classified into different groups.[2]

For practical purposes, we here classify mycobacteria on the basis of their biological behaviour, including aspects of clinical presentation, diagnosis and culture, their response to treatment and on zoonotic aspects.

Tuberculosis (TB) complex group

Mycobacterium tuberculosis (mainly infecting humans and dogs, rarely cats and other species), *M bovis* (infecting cattle, dogs and cats) and *M microti* (infecting small rodents like voles, shrews and cats) are bacteria that can be grown only in specific culture media. Tuberculosis in cats is a systemic disease with disseminated internal lesions,[3,4] but cats with *M microti* infection may also present with localised or disseminated cutaneous disease.[5]

Non-tuberculous mycobacteria (NTM) group

This group includes a large number of slow-growing species like *M mageritense*, *M genavese* and *M malmoense* and rapidly growing species like *M fortuitum*, *M chelonae-abscessus*, *M avium*, *M smegmatis*, *M flavescens* and the *M avium–intracellulare* complex (MAC) among others. NTM infections in cats are typically subcutaneous (local or disseminated), rarely progressing to systemic disease.[6] However, MAC infections, which in some classifications are included within the TB complex group, are frequently sytemic.[3,7]

Feline leprosy

The *M lepraemurium* and several other species cannot be grown in culture. Infection in cats is restricted to the skin where it produces mainly localised and rarely disseminated cutaneous nodules.[8]

European Advisory Board on Cat Diseases
www.abcd-vets.org
Corresponding author: Albert Lloret
Email: Albert.LLoret@uab.cat

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Epidemiology

The prevalence of mycobacterial infections in cats is unknown. They are considered rare, but case series or case reports from the United States, Australia, New Zealand and several European countries have been published. In recent years, more cases have been recognised, probably meaning that the infection was under-diagnosed previously.[7,9,10] A 2009 survey from diagnostic laboratories in the UK evaluating tissue samples with a histological diagnosis of mycobacterial infection showed a significant incidence of around 1%.[10]

Data on the prevalence of the different mycobacterial species are also lacking. However, a recent retrospective study from the UK evaluating 339 cases of mycobacterial disease in cats found that 53% could not be identified through culture, 19% were *M microti*, 15% *M bovis*, 7% MAC and 6% of the NTM group.[5] Most cats with mycobacterial infections have an outdoor lifestyle;[5,8] living in a non-urban area seems to increase the risk.[10] Adult tom cats seem to be predisposed to developing disease,[3,5] as are Siamese and Abyssinian breeds.[5,7,11]

TB complex group

M microti infection is mainly related to direct contact with small rodents like voles and mice.[12]

M tuberculosis infection is rare in cats, probably due to their natural resistance.[13] *M tuberculosis* and *M bovis* are directly transmitted to cats by ingestion of milk from infected cattle and by direct or environmental contact with badgers (*M bovis*).[14]

NTM group

The main risk to cats is wound contamination by mycobacteria present in the environment (soil, water and decaying vegetation).[6,9,15,16]

Feline leprosy

The main risk comes from direct contact or rodent bites, or from wound contamination by mycobacteria present in the soil or on plants.[7,17]

European Advisory Board on Cat Diseases

The European Advisory Board on Cat Diseases (ABCD) is a body of experts in immunology, vaccinology and clinical feline medicine that issues guidelines on prevention and management of feline infectious diseases in Europe, for the benefit of the health and welfare of cats. The guidelines are based on current scientific knowledge of the diseases and available vaccines concerned.

The latest version of the mycobacterioses in cats guidelines is available at www.abcd-vets.org

Pathogenesis

Mycobacteria infect the macrophage and induce granulomatous and pyogranulomatous inflammatory responses in the organs involved.[18] The mycobacterial species, route of infection and immune responses determine the extent, location and severity of the lesions.

TB complex group

The primary site of infection by *M tuberculosis* and *M bovis* may be the alimentary tract, lungs or skin.[2,15] From these sites dissemination and systemic infection may occur. Occasionally, the infection is primarily systemic.

In *M microti* infection, the portal of entry is the skin, in locations commonly affected by wild rodent bites (the face and legs).[5]

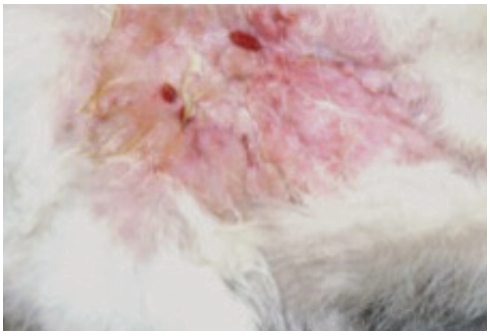


Figure 1 Mycobacterial infection in the ventral abdomen. *Courtesy of Richard Malik, University of Sydney Veterinary School*

NTM group

The primary site of infection is the skin, with mainly traumatic or surgical wounds becoming contaminated with mycobacteria.[6,8] Some fast-growing mycobacteria show a predilection to replicate in lipid-rich tissues, like the ventral abdominal and inguinal areas, particularly after a surgical wound contamination (Figure 1). A lipoid pneumonia case caused by mycobacterial infection has also been reported.[19] Dissemination from the skin and systemic infections are not common for bacteria of this group, with the exception of MAC infections, which are easily disseminated.[6,11,20–22]

Feline leprosy

The primary site of infection is the skin, with localised subcutaneous granulomas and, less commonly, disseminated skin granulomas.[7]

Clinical presentation

Most mycobacterial infections occur in immunocompetent animals.[3,5] Cases in cats with primary or acquired immunodeficiency have been documented. Two feline immunodeficiency virus-positive cats with atypical mycobacterial infection have been reported.[23,24] One case has been documented of an atypical mycobacterial infection in a cat with an idiopathic CD4+ lymphopenia.[25] Two cases (MAC disseminated infection and mycobacterial osteomyelitis) have been reported after renal transplan-

tation and long-term immunosuppressive therapy with ciclosporin.[26,27]

Cutaneous forms

M microti, the NTM group and feline leprosy species are the most common mycobacteria producing skin lesions. These typically consist of dermal nodules, non-healing wounds with draining tracts and ulceration (Figures 2–4).[4,5,8–10] Common locations are the facial area, extremities, tail base, perineum, ventral thorax and abdomen. Lesions may be solitary or multiple.[5,9] Multiple skin lesions may result from local spread or haematogenous dissemination. Local or generalised lymphadenopathy is present in about half of the cases and may be the only clinical sign (especially submandibular and prescapular).[5]

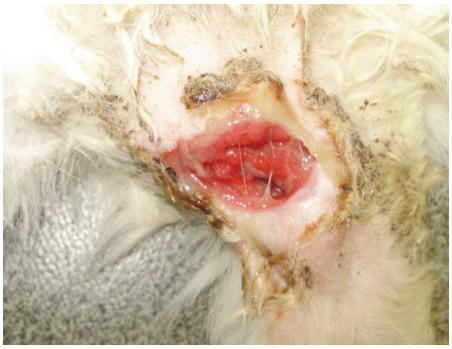


Figure 2 Ulcerated skin nodule in *M microti* infection. *Courtesy of Richard Malik, University of Sydney Veterinary School*

Figure 3 Subcutaneous skin nodule in NTM infection. *Courtesy of Albert Lloret, Veterinary Teaching Hospital, Universitat Autonoma, Barcelona, Spain*

Visceral (digestive or respiratory) or systemic forms

The TB complex and MAC species are the most common mycobacteria producing visceral or systemic lesions.[3,20–22] NTM infections rarely produce disseminated disease.[19] Common clinical signs and abnormalities are digestive (weight loss, mesenteric lymphadenopathy) or respiratory (pneumonia, hilar lymphadenopathy, pneumothorax, pleural or perdicardial effusions), and may be accompanied by signs of systemic dissemination like fever, ocular signs, splenomegaly, hepatomegaly, generalised lymphadenopathy, bone lesions and central nervous system signs.[3,6,11,20–22,27]

Diagnosis

Diagnosis may be difficult, especially when skin lesions are absent. It is based on a clinical suspicion when the presentation is indicative and other diseases are ruled out. In these cases, appropriate samples should be obtained for cytology and/or histology (including acid-fast staining), culture and polymerase chain reaction (PCR).

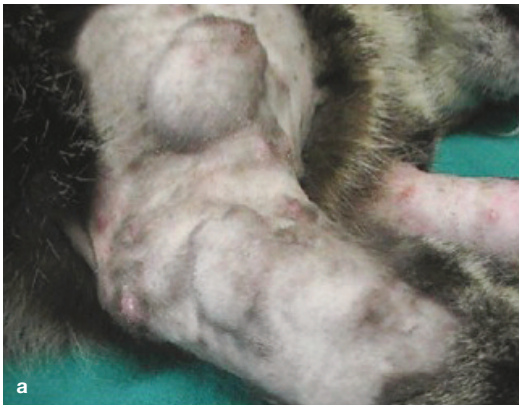
Haematology and biochemistry changes are non-specific, suggesting a chronic inflammatory condition. Hypercalcaemia due to granulomatous disease has been reported in systemic MAC[6] and *M microti* infections.[4] Cats infected with mycobacteria may show reduced levels of vitamin D when compared with healthy cats, as occurs in humans.[28]

Thoracic radiographic changes are variable and non-specific, ranging from no abnormalities to bronchial, alveolar or interstitial nodular mixed patterns, pleural effusion and/or mediastinal and perihilar lymphadenopathy (Figure 5).[29] Appendicular radiographs may show bone osteolytic lesions, and less frequently osteoproliferative changes, associated with systemic infections.[27,29] Abdominal ultrasound may be useful for identifying mesenteric lymphadenopathy or granulomatous lesions and as a guide to obtain fine needle aspirates.[26]

Cytology

Fine needle aspirates or smears from skin lesions (nodules, ulcers, draining tracts) or from granulomatous lymph nodes should always be stained for acid-fast bacteria using, for example, the Ziehl-Neelsen (ZN) procedure. Sensitivity is variable, as the number of bacteria within macrophages varies depending on the mycobacterial species and on the host's immune response.[2] A negative cytology result does not rule out mycobacterial infection [EBM grade III].[10] If cytology suggests a granulomatous inflammation, a biopsy for

EBM grades
The ranking system for grading the level of evidence of various statements within this article is described on page 533 of this Special Issue.



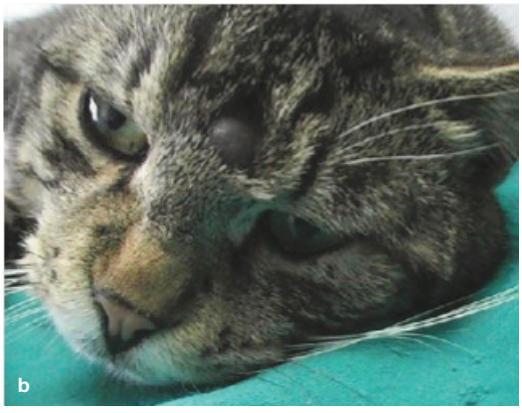


Figure 4 (a,b) Subcutaneous nodules in a cat with leprosy. *Courtesy of Richard Malik, University of Sydney Veterinary School*

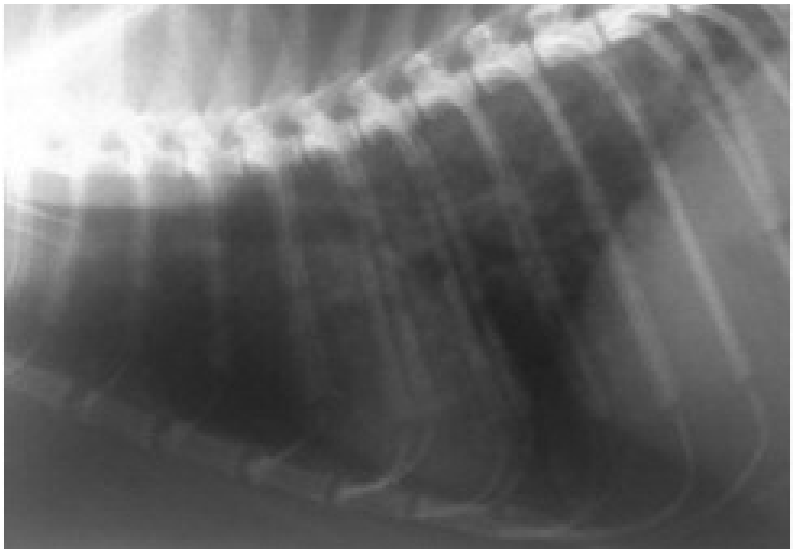


Figure 5 Mixed bronchial–interstitial pattern in the lungs of a cat with TB complex group infection. *Courtesy of Richard Malik, University of Sydney Veterinary School*

histology must be obtained. Samples for culture and PCR should be obtained in all cases when a mycobacterial infection is suspected (granulomatous inflammation and ZN-positive staining).

Histology

Histology is useful in the diagnosis of mycobacterial infections. It allows the inflammatory pattern (pyogranulomatous or granulomatous) to be assessed and special acid-fast staining, like ZN, to be performed (Figure 6).[18,30] However, only a few bacteria may be present and pass undetected by staining (*M microti* and some NTM species), although culture or PCR may give a positive result [EBM grade III].[10,30] Bacterial morphology and staining do not allow identification of the mycobacterial species. If a mycobacterial infection is suspected it is mandatory to keep fresh biopsy samples frozen for further culture and PCR.[2]

Culture

Culture from a fresh tissue sample is useful to confirm mycobacterial infection and to identify the species involved, which has implications for treatment, prognosis and assessment of zoonotic risk. This needs to be done in a specialised laboratory and, even still, many mycobacterial species are slow growing (2 to 3 months) or fail to grow [EBM grade III].[5,10] In feline leprosy and some forms of NTM infection, cultures are always negative, even when ZN staining has been positive [EBM grade III].[7,17,30] Due to these limitations it is advisable to simultaneously submit samples for PCR.

PCR

PCR (eventually followed by sequencing) is the recommended test for diagnosing mycobacterial infections [EBM grade III].[4,13,18] It allows confirmation of the diagnosis and species identification more rapidly than any other procedure. Availability may be limited depending on the private diagnostic laboratories in the area. Samples should alternatively be submitted to an official national laboratory for mycobacterial diagnosis.

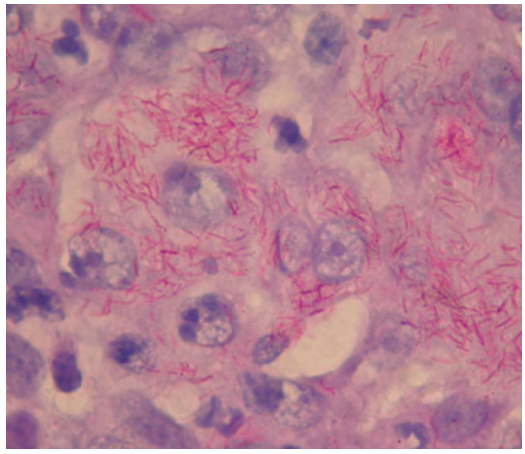


Figure 6 Large numbers of acid-fast bacteria revealed using the Ziehl–Neelsen stain. *Courtesy of Richard Malik, University of Sydney Veterinary School*

Interferon gamma test and other immunoassays

These tests are currently commercially unavailable, but they are promising for the diagnosis of TB complex group infections.[31,32] A recent study evaluating a cell-based interferon gamma test and serum antibody tests showed excellent specificity and a variable, moderate sensitivity [EBM grade II].[33]

If a mycobacterial infection is suspected it is mandatory to keep fresh biopsy samples frozen for further culture and PCR.

Important issues to consider before starting treatment

- The zoonotic risk (particularly of the TB complex group including *M microti*, and the MAC) must be discussed with the owner;[2,35] especially, but not exclusively, if the owner suffers from an immunodeficiency condition. In some cases we should advise against treating these cats.
- Confirmation (by culture or PCR) of the mycobacterial species may take time. In some instances, the zoonotic risk (in the case of *M tuberculosis* or *M bovis*) may be unacceptable, and inappropriate initial antibiotic selection may lead to the development of mycobacterial resistance.[2,30,36]
- Treatment requires several months of an antibiotic combination regimen; compliance, risk of adverse effects and financial issues must be discussed with the owner.

Treatment

Treatment of mycobacterial infections is generally difficult and challenging. There are no prospective controlled clinical trials, and recommendations are based on case reports or retrospective studies. Good outcomes have been published after identification of the mycobacterial species and treatment with a long (several months) course of an appropriate antibiotic combination [EBM grade III].[2,30] Surgery is indicated when local skin lesions can be removed; more diffuse lesions can be treated with surgical debridement and the cat subsequently treated with appropriate antibiotics [EBM grade III].[8,34]

Some important considerations before embarking on treatment are outlined in the box above.

TB complex group and NTM group

Currently, double or triple therapy is recommended: rifampicin (10–15 mg/kg q24h) plus a quinolone (marbofloxacin 2 mg/kg q24h) plus a macrolide (clarithromycin 125 mg/cat q24h or azithromycin 5–15 mg/kg q24h) for 6–9 months. Ideally, the three drugs should be giving during an initial phase of 2 months, followed by two of the drugs for 4–7 months [EBM grade III].[2,3] In many cats, an oesophageal tube is needed to allow for such long and intensive pill administration.[2] Adverse effects (cutaneous, hepatic) are not uncommon, and in some cats treatment must be discontinued.[2]

Short courses of antibiotic and/or monotherapy (eg, quinolones or beta-lactams) have been associated with clinical responses and remissions, but also with a high risk of relapse, which may be followed by systemic spread.[30] It is recommended always to start complete treatment while waiting for diagnostic confirmation and species identification.

MAC infections

Disseminated MAC infections usually respond poorly to treatment, and quinolones are not very effective [EBM grade IV].[20–22] Recommended first-line therapy is clarithromycin with clofazimine (4–8 mg/kg q24h) or rifampicin or doxycycline (5–10 mg/kg q12h) based on the few cases reported with good outcomes [EBM grade IV].[8,37,38]

Feline leprosy

Most cats with leprosy can be cured by surgery (small lesions) and applying combinations of rifampicin, clofazimine and clarithromycin for several months [EBM grade III].[1,7] Spontaneous remission has been documented in one cat [EBM grade IV].[39]

Prevention

Keeping cats indoors and avoiding contact with wild rodents are the only measures for preventing mycobacterial infection.

Prognosis

The prognosis generally must be considered guarded, but depends on the mycobacterial species and the extent and severity of the disease. Disseminated infections (TB complex and MAC) are associated with a poor prognosis.[3,9,20–22] Localised skin disease (NTM infection), *M microti* infection and leprosy may have a good prognosis if treated appropriately.[7,8,30]

Localised skin disease (NTM infection), *M microti* infection and leprosy may have a good prognosis if treated appropriately.

Zoonosis

All members of the TB complex group (including *M microti*) and the MAC are potentially zoonotic.

Potential zoonotic risk

All members of the TB complex group (including *M microti*) and the MAC are potentially zoonotic. However, the risk of transmission from cats (and dogs) to humans is low.[2,14,35] There is a single published report from Australia of a human mycobacterial infection – a case of *M marinum* (NTM group) local skin infection acquired from a cat after a scratch.[40] Conversely, cats are at risk of infection if the owner is diagnosed with tuberculosis.

The use of gloves is strongly recommended when treating cats with suspected mycobacterial infections and/or when taking and processing biopsy samples. National regulations need to be consulted to establish whether health authorities must be notified of the disease.

KEY POINTS

- Mycobacterial infections should be included in the list of differential diagnoses for cats with solitary or multiple nodules, ulcers and draining tracts, especially in 'fight and bite' locations.
- Acid-fast (eg, Ziehl-Neelsen) staining should always be performed if cytology or histology samples show a granulomatous inflammatory pattern.
- Samples for culture and/or PCR should be submitted to specialised laboratories to confirm mycobacterial infection and for species identification.
- Treatment of mycobacterial infections requires long-term therapy with a combination of two or three antibiotics in most cases. In some cases surgery may be needed as well.
- Incomplete treatment and lack of compliance may be an important cause of treatment failure and may induce resistance to antibiotics.
- Potential zoonotic risk exists with some mycobacterial species, and should be discussed with the owner before starting treatment; especially in the case of immunosuppressed persons in the household.

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Conflict of interest

The authors do not have any potential conflicts of interest to declare.

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