GUIDELINE for Mycobacterioses in cats

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Agent properties

Mycobacteria are intracellular, acid-fast, slow-growing bacilliform Gram-positive aerobic bacteria, highly resistant to environmental conditions (Greene and Gunn-Moore, 2006; Gunn-Moore, 2010). Mycobacterial taxonomy is complex, and many species can infect cats and cause different clinical presentations. Different classifications have been suggested in the past based on features and ability to growth in culture as well as biochemical properties (Gunn-Moore, 2010). The use of molecular techniques has led to taxonomic changes, and some species have been classified into different groups (Gunn-Moore, 2010).

For practical purposes, mycobacteria will be classified in this guideline on the basis of their biologic behaviour, including aspects of clinical presentation, diagnosis and culture, their response to treatment and zoonotic aspects.

Tuberculosis (TBC) complex group

This group includes *Mycobacterium tuberculosis* (mainly infecting humans and dogs, rarely cats and other species), *Mycobacterium bovis* (infecting cattle, dogs, cats and rarely humans) and *Mycobacterium microti* (infecting small rodents like voles and shrews as well as cats). These bacteria are obligate pathogens and can be grown only in specific culture media. Tuberculosis in cats most commonly arises due to *M. bovis or M. microti* infections. Infection with these species can result in systemic disease with disseminated internal lesions (mainly digestive or respiratory), especially with *M. bovis* (Gunn-Moore et al., 1996; Rüfenacht et al., 2011); infections with *M. microti* are more commonly associated with localized or disseminated cutaneous disease (Gunn-Moore et al., 2011a).

Nontuberculous mycobacteria (NTM) group

This group includes a large number of species that have pathogenic potential but are generally saprophytic or opportunistic. NTM slow-growing and rapid-growing species causing infections in cats are listed in Table 1. NTM infections in cats typically involve skin and subcutaneous tissues (either focal, multifocal or diffuse lesions), rarely progressing to systemic disease (Baral et al., 2006; Pekkarinen et al., 2018) with the exception of MAC (*Mycobacterium avium-intracellulare* complex) infections, which are more frequently systemic in nature (Gunn-Moore et al., 1996; Malik et al., 2002; Munro et al., 2021).

Feline leprosy

Mycobacterium lepraemurium, and several other species that cause feline leprosy, cannot be grown in culture. Infection in cats is restricted to the skin where it produces localized and rarely disseminated cutaneous nodules (Horne and Kunkle, 2009; O'Brien et al., 2017a, b, c; Krug et al., 2018).

Knowledge on this group of species is evolving rapidly, particularly in Australia and New Zealand where most cases are diagnosed and reported. Novel species and associated disease have been detected in recent years, such as 'Candidatus *Mycobacterium tarwinense*' and 'Candidatus *Mycobacterium lepraefelis*' (O'Brien et al., 2017a, c) (Table 1).

MYCOBACTERIA SPECIES	TRANSMISSION	CLINICAL PRESENTATION	TREATMENT	ZOONOTIC RISK REFERENCES

MYCOBACTERIA SPECIES	TRANSMISSION	CLINICAL PRESENTATION	TREATMENT	ZOONOTIC RISK REFERENCES
Tuberculosis complex				
Mycobacterium tuberculosis	Inhalation respiratory secretions from infected humans	Pulmonary Mesenteric / gastrointestinal Lymphadenopathy Systemic	Not advised	Anthropozoonosis Cats naturally resistent
Mycobacterium bovis	Ingestion unpasteurized milk Ingestion or contact with wild species (badgers) Cutaneous inoculation contaminated soil Cat-to-cat Commercial raw food	Cutaneous lesions (nodules, ulcers) Lymphadenopathy Mesenteric / gastrointestinal Ocular lesions Systemic disease	Clarithromycin (azithromycin), pradofloxacin and rifampicine Surgical removal skin nodules Other alternative drugs in some cases	Potential zoonotic risk (low) Humans infected by cats in two reports O'Connor et al., 2019 Attig et al., 2019 Cerna et al., 2019 O'Halloran et al., 2019 Murray et al., 2015 Ramdas et al., 2015
Mycobacterium microti	Ingestion or contact with prey species, (voles, mice) Cutaneous inoculation contaminated soil	Localized or generalized cutaneous lesions (nodules, ulcers) Lymphadenopathy	Same	Low potential risk In immuno-competent humansRüfenacht et al., 2011 Smith et al., 2009 Gunn-Moore et al., 1996
Nontuberculous mycobacterial disease (NTM)				
Slow-growing bacteria				
Mycobacterium avium-intracellulare complex (MAC)	Cutaneous inoculation contaminated cat fights Ingestion of contaminated water or prey species (birds)	Mesenteric lymphadenopathy Pulmonary Systemic involvement Ocular lesions Meningoencephalitis Maybe associated with immunodeficiency in some cats Breed predisposition	Clarithromycin (azithromycin) and one or two of the following pradofloxacin, rifampicine or clofazimine	Low potential risk In immuno-competent humansPekkarinen et al., 2018 Madarame et al., 2017 Rivière et al., 2011 De Groot et al., 2010 Sieber-Ruckstuhl et al., 2007 Baral et al., 2006 Griffin et al., 2003 Kaufman et al., 1995 Jordan et al., 1994
Mycobacterium genavense		Respiratory and systemic in a FIV cat		Hughes et al., 1999
Mycobacterium malmoense		Local muscular Disseminated disease	Enrofloxacin, rifampicin and azithromycin	Pekkarinen et al., 2018 Hetzel et al., 2012

MYCOBACTERIA SPECIES	TRANSMISSION	CLINICAL PRESENTATION	TREATMENT	ZOONOTIC RISK REFERENCES
Mycobacterium celatum				
Mycobacterium terrae		Skin nodule	Enrofloxacin, rifampicin, clarithromycin	Henderson et al., 2003
Mycobacterium simiae				Dietrich et al., 2003
Mycobacterium xenopi		Tracheal granuloma in a FIV cat Chronic disseminated in a cat with primary CD4+ lymphocytopenia Peritonitis and lymphadenopathy	Surgery Enrofloxacin, rifampicin, clarithromycin, clofazimide	De Lorenzi and Solano-Gallego, 2009 Meeks et al., 2008 MacWilliams et al., 1998
Mycobacterium ulcerans		Skin nodule	Surgery clarithromycin	Elsner et al., 2008
Mycobacterium heckeshornense		Gastrointestinal and systemic disease in a FIV cat		Elze et al., 2013
Mycobacterium branderi/shimoidei		Disseminated disease		Pekkarinen et al., 2018
Mycobacterium kansasi		Systemic		Lee et al., 2017
Mycobacterium sp strain MFM001	Unknown, water suggested	Gastrointestinal and systemic disease in an immunosuppressed cat		Kayanuma et al., 2019
Mycobacterium nebraskense		Nodular skin lesions, panniculitis	Clarithromycin Rifampicin Surgery	Niederhäuser et al., 2018
Rapid-growing bacteria				
Mycobacterium fortuitum	Cat bite	Skin lesions, panniculitis Respiratory disease	No response	Ngan et al., 2005 Jang and Hirsch, 2002 Krajewska-Wędzina et al., 2019 Couto and Artacho, 2007
Mycobacterium chelonae-abscessus		Skin lesions		Jang and Hirsch, 2002
Mycobacterium mageritense		Skin lesions		Govendir et al., 2011a, b
Mycobacterium smegmatis		Skin lesions Panniculitis		Bennie et al., 2015 Alander-Damsten et al., 2003
Mycobacterium flavescens		Skin lesions		Jang and Hirsch, 2002

MYCOBACTERIA SPECIES	TRANSMISSION	CLINICAL PRESENTATION	TREATMENT	ZOONOTIC RISK REFERENCES
Mycobacterium mucogenicum				
Mycobacterium massiliense		Skin lesions		Albini et al., 2007
Mycobacterium phlei				
Mycobacterium thermoresistible	Contamination by soil	Panniculitis in surgical wounds		No Vishkautsan et al., 2016 Suy et al., 2013 Foster et al., 1999 Willemse et al., 1985
Mycobacterium porcinum		Panniculitis	Pradofloxacin and doxycycline	Cox and Udenberg, 2020 Mannion et al., 2020
Feline leprosy syndrome				
Mycobacterium lepraemurium	Rodent bites Soil contamination	Skin nodules head and forelimbs Rarely disseminated skin nodules	Surgical excision Two or three of the following drugs: rifampicin, clofazimine, clarithromycin, Pradofloxacin Spontaneous remission in some cats	No zoonotic risk No cat-to-cat transmission Krug et al., 2018 O'Brien et al., 2017b Malik et al., 2002 Roccabianca et al., 1996
Candidatus "Mycobacterium tarwinense"	Cat aggression Self-inoculation grooming Rodent bites Soil contamination	Ocular lesions (proliferative lesions in conjunctiva, cornea, eyelids, nictitating membrane) Nasal and periocular skin nodules Forelimbs nodules	Surgical excision (especially cornea) Two or three of the following drugs: rifampicin, clofazimine, clarithromycin, Pradofloxacin	No zoonotic risk O'Brien et al., 2017c
Candidatus "Mycobacterium lepraefelis"	Cat aggression Rodent bites	Skin nodules with tendency to progress to generalized skin disease Systemic involvement and haematogenous dissemination	Poor response to treatment Surgical excision and/or debulking of lesions Two or three of the following drugs; dapsone, rifampicin, clofazimine, moxifloxacin, minocycline	No zoonotic risk O'Brien et al., 2017a Malik et al., 2002

Epidemiology

The true prevalence of mycobacterial infections in cats is unknown. They are considered rare, but case series or case reports from the USA, Australia, New Zealand and several European countries have been reported or published. In recent years, more cases have been recognised, suggesting that infection has been under-diagnosed previously (Malik et al., 2002; Smith et al., 2009; Gunn-Moore et al., 2013). A survey (2009) from diagnostic laboratories in the UK evaluating the prevalence of tissue samples with a final histological

diagnosis of mycobacterial infection showed a relatively high incidence of approximately 1% (Gunn-Moore et al., 2013).

Data on the importance of the different mycobacterial species are also lacking. A retrospective study from the UK, evaluating 339 cases of mycobacterial disease in cats, found that 53% could not be identified following culture; 19% were *M. microti*, 15% *M. bovis*, 7% MAC and 6% NTM (Gunn-Moore et al., 2011a). Most cats with mycobacterial infections have an outdoor lifestyle (Horne and Kunkle, 2009; Gunn-Moore et al., 2011a), but infection has also been reported in indoor cats. Living in a non-urban area seems to increase the risk of infection (Gunn-Moore et al., 2013). Adult male cats are likely predisposed to become infected (Gunn-Moore et al., 1996; Gunn-Moore et al., 2011a), and Siamese, Somali and Abyssinian breeds seem to be predisposed specifically for MAC infections (Malik et al., 2002; Burthe et al., 2008; Gunn-Moore et al., 2011a).

Tuberculosis complex group

M. microti infection is mainly related to ingestion or direct contact (bites) with small rodents like voles and mice (Aranaz et al., 1996). *M. tuberculosis* infection is rare in cats (Hartmann et al., 2000), probably due to their natural resistance to infection (Biet et al., 2005). *M. tuberculosis* and *M. bovis* can be directly transmitted to cats by several methods such as direct contact with an infected human (*M. tuberculosis*), ingestion of milk from infected cattle or by direct or environmental contact with badgers (*M. bovis*; Malik et al., 2000).

M. bovis infection can also be transmitted cat-to-cat by direct contact as it has been reported in recent years. In the UK, a nosocomial infection with *M. bovis* was reported in a cluster of cats which had attended a veterinary practice in Ireland for routine surgery (Murray et al., 2015). In a recent outbreak in Italy, five indoor Abyssinian cats living in a breeding cattery were infected by a kitten imported from Ukraine. All of the cats died with respiratory, gastrointestinal and systemic clinical signs (Černá et al., 2019).

Recently, several cats have been diagnosed with *M. bovis* infection associated with the ingestion of a commercial raw food. Thirteen indoor cats in 5 different households from different areas were diagnosed with mycobacteriosis by culture, PCR and/or interferon-gamma release assay (IGRA). Six cats were presented with severe clinical disease, five of them dying. Seven cats tested positive by IGRA without showing clinical signs at the time the report was submitted for publication. Following publication, the authors identified up to 30 more infected cats. All the cats had been fed with the same raw food and so, while still not definitively proven, the food was the likely source of *M. bovis* infection. No cat-to-owner transmission was reported so far associated with those outbreaks (O'Halloran et al., 2019).

NTM group

The main risk for infection with these species is wound contamination by NTM present in the environment, soil, water and in decaying vegetation (Jang and Hirsch, 2002; Baral et al., 2006; Smith et al., 2009).

Infection with MAC species can also be acquired by ingestion or contact with prey species such as birds (*M. avium* subsp. *avium*).

Feline leprosy

The main risk for infection with leprosy-causing bacteria is direct contact or rodent bites, but infection can also result from wound contamination by mycobacteria present in soil or on plants (McIntosh, 1982; Horne and Kunkle, 2009).

Other means of transmission, such a cat fights and grooming, have been proposed for *Candidatus* "Mycobacterium tarwinese" (O'Brien et al., 2017c).

Pathogenesis

Mycobacteria infect macrophages and induce granulomatous and pyogranulomatous inflammatory responses to the affected persistent stimuli of the pathogen in the organs (Kipar et al., 2003; O'Halloran et al., 2018). The mycobacterial species, route of infection and immune responses determine the extent, location and severity of the lesions.

The inflammatory cascade induced by mycobacterial infection is complex and poorly characterised in the cat. Inhibition of phagosome-lysosome fusion enables the intracellular survival of mycobacteria which stimulates macrophage invasion of tissues. Cytokine production is also stimulated, predominantly TNF-α, which drives the recruitment of mononuclear cells and neutrophils from surrounding blood vessels. Additionally, each group of recruited cells also releases its own assortment of cytokines and chemokines, which perpetuate the inflammatory cascade and lead to the formation of stable granuloma (O'Halloran et al., 2018).

The cytokine pattern in feline mycobacterioses has recently been studied for the first time, revealing that seven critically important cytokines were increased (GM-CSF, IL-2, PDGF-BB, IL-8, KC, RANTES and TNF-α) compared to control cats (healthy cats and ill cats with other diseases), showing a sensitive and specific cytokine indication/pattern of mycobacterial infection in this study population. Three cytokines were significantly reduced (sFAS, IL-13 and IL-4). This pattern is suggestive of a pro-inflammatory process which is dominated by the recruitment and maturation of monocyte-macrophage lineage cells, the recruitment of cytotoxic T-cells, the proliferation of

fibroblasts and the suppression of humoral immunity. These results were obtained retrospectively from a small number of cats. Further prospective studies are required to evaluate whether the cytokine pattern could be of diagnostic use for feline mycobacteriosis. For example, TBC infections seemed to be associated with significant elevations of GM-CSF, IL-2 and Flt3-L, in contrast to NTM infections (O'Halloran et al., 2018).

Tuberculosis complex group

The primary site of infection by *M. tuberculosis* and *M. bovis* can be the alimentary tract, the lungs or skin (Malik et al., 2000; Gunn-Moore, 2010), largely dependent on the route of infection (ingestion, inhalation or contact, respectively). From these sites, dissemination and systemic infection can occur, e.g. haematogenous spread to the lungs from cutaneous lesions. Only rarely is the infection primarily systemic. With *M. microti* infection the route of entry is the skin, in locations commonly affected by wild rodent bites (the face and legs) (Gunn-Moore et al., 2011a).

NTM group

The primary site of infection is the skin, mainly through traumatic or surgical wounds contaminated with mycobacteria (Baral et al., 2006; Smith et al., 2009; Vishkautsan et al., 2016). Some fast-growing mycobacteria show a predilection to replicate in lipid-rich tissues, such as the ventral abdominal and inguinal areas, particularly after surgical wound contamination, causing cutaneous panniculitis (Fig. 1).

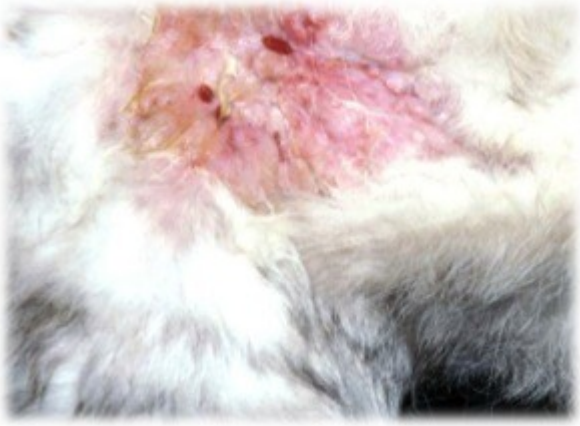

Fig. 1. Mycobacterial infection in ventral abdomen (courtesy Richard Malik, University of Sydney Veterinary School)

A case of lipoid pneumonia caused by mycobacterial infection has been reported (Couto and Artacho, 2007). Dissemination from the skin and systemic infections are not commonly caused by bacteria of this group, with exception of MAC infections which easily disseminate (Jordan et al., 1994; Barry et al., 2002; Malik et al., 2002; De Groot et al., 2010; Rivière et al., 2011). However, a recent paper reported three cats with NTM disseminated infections (respiratory, gastrointestinal) in immunocompetent cats (Pekkarinen et al., 2018).

Feline leprosy

The primary site of infection is the skin, with localised subcutaneous granulomas and less commonly disseminated skin granulomas (Horne and Kunkle, 2009).

Clinical signs

Although there are some trends in clinical manifestations associated with the type of mycobacterial species involved, it should be noted that it is not possible to determine the mycobacterial species based on clinical presentation alone.

Most mycobacterial infections occur in immunocompetent animals (Gunn-Moore et al., 1996; Gunn-Moore et al., 2011a). Cases in cats with primary or acquired immunodeficiency, such as with retrovirus infection, have been reported with disseminated MAC infections and NTM slow-growing mycobacterial infections (Hughes et al., 1999; De Lorenzi and Solano-Gallego, 2009). One case of an atypical

mycobacterial infection in a cat with an idiopathic CD4+ lymphopenia was documented (Meeks et al., 2008). Two cases (MAC disseminated infection and mycobacterial osteomyelitis) have been reported after renal transplantation and long-term immunosuppressive therapy with cyclosporine (Griffin et al., 2003; Lo et al., 2012). One case of disseminated *M. avium* subspecies *hominissuis* associated with ascites in a feline immunodeficiency virus infected cat has been described (Paharsingh et al., 2020).

Cutaneous forms

M. microti, the NTM mycobacteria and feline leprosy species are the most common mycobacteria producing skin lesions. These commonly consist of dermal nodules, non-healing wounds with draining tracts and ulceration (Baral et al., 2006; Horne and Kunkle, 2009; Smith et al., 2009; Gunn-Moore et al., 2011a; Gunn-Moore et al., 2013) (Figs. 2, 3, 4).

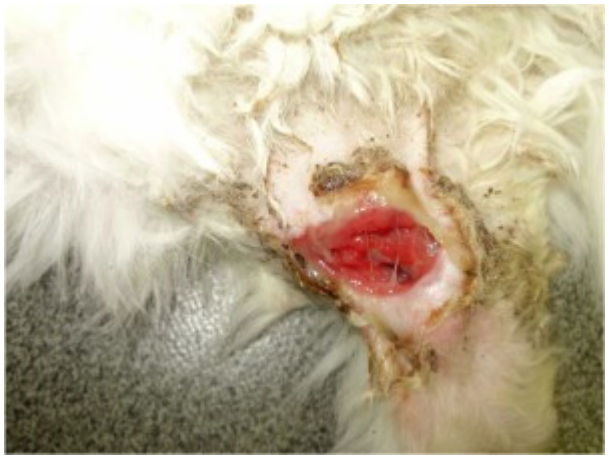

Fig. 2. Ulcerated skin nodule in M. microti (courtesy of Richard Malik, University of Sydney Veterinary School)

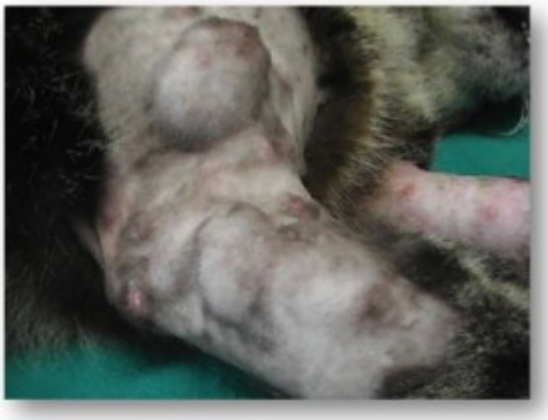

Fig. 3. Subcutaneous nodules in lepra (courtesy of Richard Malik, University of Sydney Veterinary School)

Fig. 4. Subcutaneous nodules in lepra (courtesy of Richard Malik, University of Sydney Veterinary School)

Common locations are the facial area, extremities, tail base, perineum, ventral thorax and abdomen. Lesions can be solitary or multiple (Smith et al., 2009; Gunn-Moore et al., 2011a). Multiple skin lesions can result from local spread or haematogenous dissemination. Local or generalised lymphadenopathy is present in about half of the cases and can be the only clinical sign (especially submandibular and praescapular) (Gunn-Moore et al., 2011a).

Visceral (gastrointestinal or respiratory) or systemic forms

The TB complex and MAC species are the most common mycobacteria producing visceral or systemic lesions (Gunn-Moore et al., 1996; Barry et al., 2002; De Lorenzi and Solano-Gallego, 2009; De Groot et al., 2010; Rivière et al., 2011). NTM and leprosy infections rarely produce disseminated disease (Couto and Artacho, 2007), but several case reports of disseminated infection have been reported, even in immunocompetent cats (Lee et al., 2017; O'Brien et al., 2017a; Pekkarinen et al., 2018). Common clinical signs and abnormalities include gastrointestinal (weight loss, mesenteric lymphadenopathy) or respiratory (pneumonia, hilar lymphadenopathy, pneumothorax, pleural or pericardial effusions) signs which can be accompanied by signs of systemic infection such as fever, ocular signs, splenomegaly, hepatomegaly, generalised lymphadenopathy, bone lesions and neurological signs (Hartmann et al., 2000; Barry et al., 2002; Malik et al., 2002; Burthe et al., 2008; De Groot et al., 2010; Rivière et al., 2011; Rüfenacht et al., 2011; Lo et al., 2012; Madarame et al., 2017).

Neurological disease is usually present in cats with systemic involvement and other clinical signs, but one cat was reported that was presented only with neurological signs due to a pyogranulomatous meningoencephalitis by *M. avium subspecies hominissuis*. However, following necropsy and histopathological studies, mycobacteria were identified in several organs, and granulomatous lymphadenitis was evident (Madareme et al., 2017).

Recently a case series of feline ocular mycobacteriosis has been published. Approximately 25% of the cats were presented only with ocular signs, emphasizing the importance of including these infections in the differential list of potential causes, not only in cats with systemic disease with ocular signs, but also in cats with only ocular signs. The most common ocular signs were uveitis and blindness, but some cats also showed corneal, conjunctival and eyelid proliferative lesions. Cataracts, lens subluxation and glaucoma secondary to uveitis were present in some cats. In 80% of the cats, ocular disease was unilateral at presentation (Stavinohova et al., 2019).

Cats in recent outbreaks of *M. bovis* infection associated with contaminated raw food were presented with unusual, severe and rapidly progressive clinical disease; and there was a high mortality rate even after attempting treatment. Hence, gastrointestinal infection seems to produce more severe disease compared to infections associated with skin exposure. It has been suggested also that these aggressive infections might be caused by more virulent *M. bovis* strains (O'Halloran et al., 2019).

Diagnosis

Diagnosis can be difficult, especially when skin lesions are absent, and is based on a clinical suspicion when the presentation is indicative and other diseases have been ruled out. The traditional tuberculin skin-testing technique used in other species is insensitive in domestic cats (Broughan et al., 2013). Therefore, appropriate samples should be collected for cytology and/or histology (including acid-fast staining), culture and PCR. An interferon-gamma release assay (IGRA) is available in some countries and can be used when cytology samples are non-diagnostic, or tissue samples are not available.

Haematology and biochemistry changes are non-specific, suggesting a chronic inflammatory condition. Hypercalcaemia due to granulomatous disease has been reported with systemic MAC (Malik et al., 2002) and *M. microti* infections (Gunn-Moore et al., 2011a). Cats infected with mycobacteria can show reduced levels of vitamin D compared to healthy cats, as occurs in humans (Lalor et al., 2012), although the clinical significance of this is unknown.

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 (Bennet et al., 2011) (Fig. 5). Appendicular radiographs can show bone osteolytic lesions, and (less frequently) osteoproliferative changes, associated with systemic mycobacterial infections (Bennet et al., 2011; Lo et al., 2012). Abdominal ultrasonography can be useful to find mesenteric lymphadenopathy or granulomatous lesions and as a guide to obtain fine needle aspirates (Griffin et al., 2003).

CT scan abnormalities were also reported in a group of 20 cats with mycobacterial infections. Interstitial lung pattern, mediastinal and/or mesenteric lymphadenomegaly and osteolytic or proliferative skeletal lesions were the most frequent abnormalities seen (Major et al., 2016).

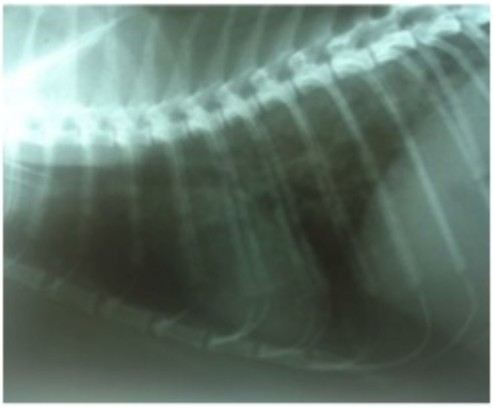

Fig. 5. Mixed bronchial-interstitial pattern in the lung of a cat with tuberculosis complex group infection (courtesy of Richard Malik, University of Sydney Veterinary School)

Cytology

Fine needle aspirates or smears from skin lesions (nodules, ulcers, draining tracts) or granulomatous lymph nodes should always be stained for acid-fast bacteria using e.g. Ziehl-Nielsen (ZN) staining. The sensitivity is variable, however, as the number of bacteria within macrophages varies depending on the mycobacterial species and on the host's immune response to infection (Gunn-Moore, 2010). A negative cytology result does not rule out mycobacterial infection (Gunn-Moore et al., 2013). If cytology suggests granulomatous inflammation, a biopsy for histology should be obtained, as well as samples for culture and PCR if mycobacterial infection is suspected (e.g. granulomatous inflammation with or without ZN-positive staining).

Histology

Histology is useful for the diagnosis of mycobacterial infections. It allows the assessment of the inflammatory pattern, which can vary depending on the mycobacterial species involved (pyogranulomatous or granulomatous inflammation, presence of granulation tissue and/or mixed inflammatory response, necrosis, panniculitis), and allows acid-fast staining such as with ZN (Kipar et al., 2003; Gunn-Moore et al., 2011b) (Fig. 6). However, sometimes only a few bacteria are present and they are not detected by ZN staining (particularly with infections of *M. microti* and some NTM rapid-growing species), although culture or PCR may still give a positive result in such cases (Gunn-Moore et al., 2011b; Gunn-Moore et al., 2013). Bacterial morphology and staining do not allow the identification of the mycobacterial species. If mycobacterial infection is suspected, it is mandatory to keep fresh biopsy samples frozen without formalin for subsequent culture and PCR (Gunn-Moore, 2010); formalin can affect PCR sensitivity and prevents subsequent culture from the sample, so it is imperative that samples are kept frozen without preservative in case culture and/or PCR are needed after the histology results have been obtained.

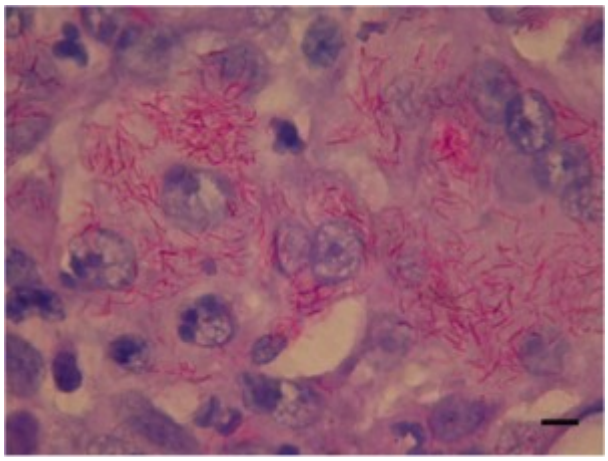

Fig. 6. Large numbers of acid-fast bacteria as shown using the Ziehl–Neelsen stain (courtesy of Richard Malik, University of Sydney Veterinary School)

Culture

A positive culture from a fresh tissue sample or fine needle aspirates is useful to confirm mycobacterial infection and to identify the species involved, which has implications for treatment, prognosis and assessment of zoonotic risk. Culture is the gold standard method of diagnosis for the mycobacteria species that can be grown in culture, such as the TBC species and some NTM species. However, culture needs to be done in a specialised laboratory under containment. Many mycobacterial species need a long time to grow in culture (2 to 3 months) or even fail to grow (Malik et al., 2000; Gunn-Moore et al., 2011a; Gunn-Moore et al., 2013). It is important to contact a specialised laboratory to ask for the correct procedures and requirements for sample submission. In feline leprosy and some forms of NTM infection, cultures are always negative, even when ZN staining has been positive (Gunn-Moore et al., 2011b). Due to these limitations, it is advisable to simultaneously submit fresh samples for PCR.

Polymerase chain reaction (PCR)

PCR (followed by sequencing, if available) is the recommended test for the rapid diagnosis of mycobacterial infections (Kipar et al., 2003; Biet et al., 2005; Rüfenacht et al., 2011). It allows confirmation of the diagnosis and species identification more rapidly than any other procedure and is especially useful for species that cannot be grown in culture. The availability of PCR testing can be limited, depending on the commercial diagnostic laboratories in the area; otherwise samples should be submitted to an official national human laboratory for mycobacterial diagnosis. Fresh tissue samples are preferred for PCR testing, but frozen tissue samples, fine-needle aspirates (stained), cytology slides and formalin-fixed paraffin-embedded tissues have also been used to generate positive results if fresh tissue is not available (Reppas et al., 2013).

Interferon-gamma release assay (IGRA)

This test is currently commercially available mainly in the UK, although samples can be submitted from abroad. Interferon-gamma testing is useful for the diagnosis of TB complex group infections and can reduce the lag time between clinical presentation and diagnosis. The test is based on specific mycobacterial proteins being used to stimulate the cat's heparinised peripheral mononuclear cells (PBMCs). If the cat has been previously infected with the mycobacterial organism containing these peptides, IFN-γ is released by the PBMCs and detected by the IGRA. As well as being quicker, it is also cheaper than culture, PCR and sequencing and can be performed using a blood sample. The assay has been validated for diagnostic use in cats with good sensitivity (around 90%) reported to diagnose TBC infections (O'Halloran and Gunn-Moore, 2017; O'Halloran et al., 2018). In addition, it allows discrimination between *M. bovis*, *M. microti* and *M. avium* infection. IGRA can be positive in clinically healthy cats, meaning that the cat has been exposed to the mycobacteria, so results should be interpreted together with the clinical signs (Rhodes et al., 2008; Fenton et al., 2010; O'Halloran et al., 2018; O'Halloran et al., 2020). Although very helpful, IGRA is not yet regarded as a gold standard method for the definitive diagnosis of mycobacterial infection, compared to a positive culture or PCR (with sequencing if needed). The test may also be useful for monitoring treatment and validation testing for this is underway (O'Halloran and Gunn-Moore, 2017)

Treatment

Treatment of mycobacterial infections is generally challenging. There have been no prospective, controlled clinical trials, and recommendations are based on case reports or retrospective studies. Good outcomes have been reported after identification of the mycobacterial species and treatment with a long (several months) course of an appropriate antibiotic combination (Gunn-Moore, 2010). Surgery is indicated when local skin lesions can be removed; more diffuse lesions can be treated with surgical debridement and subsequent antibiotic treatment (Baral et al., 2006; Elsner et al., 2008; Horne and Kunkle, 2009).

Before starting mycobacterial treatment, four important issues must be considered:

- Firstly, the zoonotic risk (particularly for the TB complex group including *M. microti,* but also for MAC) must be discussed with the owner (Emmanuel et al., 2007; Gunn-Moore, 2010), especially, but not only, if the owner is immunocompromised or if there are very young or old people in the household. In such cases, treatment of the cat might not be recommended, and euthanasia might be considered as an option.
- Secondly, confirmation (by culture or PCR) of the mycobacterial species might take time; in this case, the zoonotic risk (especially in the case of *M. tuberculosis* (which is very rare in cats) or *M. bovis* (more commonly encountered in cats) can be unacceptable, and inappropriate initial antibiotic selection can lead to the development of mycobacterial resistance (Masur, 1993; Gunn-Moore, 2010; Gunn-Moore et al., 2011b; Gunn-Moore et al., 2013).
- Thirdly, treatment requires several months of an antibiotic combination regime; compliance, adverse effects and financial issues must be discussed with the owners.
- Fourthly, a final diagnosis should always be based on culture and/or PCR tests, but in some situations the clinical context and IGRA can be helpful to indicate the mycobacteria species involved and to evaluate the zoonotic risk and guide initial treatment. For example, in non-TB endemic areas, cats with mycobacterial infection will be less of a zoonotic risk, especially if the lesions are cutaneous with no evidence of systemic infection, and cats with diffuse panniculitis due to rapidly growing mycobacteria species pose less of a zoonotic risk.

Tuberculosis complex group and NTM group

For the tuberculosis complex and non-tuberculous mycobacteria (NTM) groups, double or triple therapy is currently recommended: rifampicin (10 to 15 mg/kg q24h) plus a fluoroquinolone (marbofloxacin 2 mg/kg q24h; or pradofloxacin 3 to 5 mg/kg q24h) plus a macrolide (clarithromycin125 mg/cat q24h or 7 to 15 mg/kg q24h; or azithromycin 5 to 15 mg/kg q24h) for 6 to 9 months. Ideally, the three drugs (triple therapy) should be administered during an initial phase for 2 months, followed by two of the drugs (dual therapy) for 4 to 7 months (Baral et al., 2006; Gunn-Moore et al., 2011a) (EBM grade III) (Gunn-Moore et al., 1996; Gunn-Moore, 2010).

The newer fluoroquinolones (moxifloxacin and pradofloxacin) might be more effective than older ones (Malik et al., 2002; Horne and Kunkle, 2009). Unpublished clinical experience suggests that pradofloxacin is a good choice; in confirmed localised disease, pradofloxacin could be a good initial treatment pending species confirmation (Smith et al., 2009) (EBM grade IV), but multiple antibiotic therapy is often indicated for mycobacterial treatment pending confirmation of diagnosis to avoid resistance developing (see below).

Recently alternative treatment courses to the original course of triple therapy for two months and then dual therapy for 4 to 7 months have been suggested. The alternatives comprise either triple therapy for 3 months alone or triple therapy given for 2-3 months beyond resolution of clinical signs or beyond static thoracic imaging abnormalities. The latter alternative course typically comprises 4 to 6 months of treatment in total and has been described as unpublished observations for the treatment of TB in cats (Major et al., 2018; O'Halloran and Gunn-Moore, 2019;). However, follow up information on this protocol is not yet available. The rationale for this treatment protocol is based on recommendations from human medicine where at least 3 or 4 antibiotics are given in combination to reduce the development of multi-drug resistant mycobacteria.

Treatment of NTM infections is ideally based on individual culture and sensitivity tests, as different mycobacterial species or strains can have different antibiotic sensitivity (Munro et al., 2021). However, this is not always possible, as specific culture systems are unavailable or results take too long.

Surgical debridement or excision are needed in some skin cases along with the multiple antibiotic therapy.

In some cats, an oesophageal feeding tube is needed to allow prolonged and intensive drug administration (Gunn-Moore, 2010). Reformulations of drugs (e.g. rifampicin and azithromycin) into one capsule are available from some manufacturers to allow for easier

dosing. Alternatively, tablets can be combined into a single gelatine capsule. Adverse effects (cutaneous, hepatic) are not uncommon, and in some cats treatment must be discontinued (Gunn-Moore, 2010). Short courses of antibiotic and/or monotherapy (e.g. quinolones or beta-lactams) have been associated with clinical responses and remissions, but also with a high risk of relapse, which can be followed by systemic spread and possible mycobacterial antibiotic resistance (Gunn-Moore et al., 2011b). It is therefore recommended to always start complete multiple antibiotic treatment whilst awaiting diagnosis confirmation and species identification.

MAC infections

Disseminated MAC infections usually respond poorly to treatment, and old generation fluoroquinolones are not very effective (Jordan et al., 1994; Burthe et al., 2008; Gunn-Moore et al., 2013). The recommended first choice treatment is clarithromycin (dose given above) with clofazimine (4 to 8 mg/kg q24h) or rifampicin (dose given above) or doxycycline (5 mg/kg q12h or 10 mg/kg q24h), based on the few cases reported with good outcomes (Kaufman et al., 1995; Aranaz et al., 1996; Malik et al., 2000; Biet et al., 2005; Sieber-Ruckstuhl et al., 2007) (EBM grade IV). Limited clinical experience with pradofloxacin suggests that it is more effective than the older fluoroquinolones (Smith et al., 2009) although resistance to fluoroquinolones and aminoglycosides was found to be common among *M. avium* isolates (Munro et al., 2021).

Feline leprosy

Most cats with leprosy due to *M lepraemurium* can be cured by surgery (small lesions) together with combinations of rifampicin, clofazimine and clarithromycin for several months (Greene and Gunn-Moore, 2006; Horne and Kunkle, 2009). Spontaneous remission has been documented in one cat (Roccabianca et al., 1996).

Prevention

Keeping a cat indoors and avoiding contact with wild rodents are the only measures for preventing mycobacterial infection. Based on recent *M. bovis* infection in UK associated with commercial raw food contamination, feeding raw diets should be avoided.

Prognosis

Prognosis must be considered guarded in general but depends on the mycobacterial species and the extent and severity of the disease. Disseminated infections (TBC, MAC and '*Candidatus* M. lepraefelis' species) are associated with a poorer prognosis (Gunn-Moore et al., 1996; Barry et al., 2002; De Lorenzi and Solano-Gallego, 2009; Smith et al., 2009; De Groot et al., 2010; Rivière et al., 2011). Localised skin disease due to NTM, *M. microti* infections and leprosy can have a good prognosis if treated properly (Baral et al., 2006; Horne and Kunkle, 2009; Gunn-Moore et al., 2011b).

Zoonotic risk

All members of the TBC complex are potentially zoonotic, including *M. microti*. However, the risk of transmission from cats (and dogs) to humans is low, as cats are spillover hosts (Biet et al., 2005; Baral et al., 2006; Couto and Artacho, 2007).

An unusual cluster of *M. bovis* infection in cats was reported from the UK in 2012 to 2013. Cat-to-cat transmission was suspected, and zoonotic infection of two humans was documented (O'Connor et al., 2019). Similarly, cat-to-human transmission was suspected in Texas, USA (Ramdas et al., 2015).

After documented evidence of cat-to-human transmission, the risk of spread of *M. bovis* from cats to their human contacts was increased from negligible to very low (Human Animal Infections and Risk Surveillance (HAIRS) Group, 2014). Cats with clinical signs compatible with disseminated disease are believed to pose the greatest risk to humans, most likely by ingestion from a contaminated environment, following handling of discharges from exudative tuberculous lesions, or by aerosols from cats with respiratory signs or aerosol-generating procedures.

As an example, Public Health England in the UK now advises that all close contacts of household companion animals with confirmed *M. bovis* infections should be assessed by a public health professional and receive guidance on how best zoonotic transmission can be minimised. In addition, as part of an enhanced surveillance system in England and Wales, newly diagnosed human patients with *M. bovis* infection are asked explicitly about contact with pets with suspected or confirmed *M. bovis* disease (O'Connor et al., 2019). Similar follow-up likely exists in other countries.

In summary, *M. bovis* disease in companion animals, particularly cats with severe systemic features including exudative lesions, can have to be regarded as posing a significant public health risk. Cats with clinical signs of disseminated disease are the greatest risk to humans by ingestion from a contaminated environment and/or by aerosols from cats.

Euthanasia or treatment of cats with confirmed *M. bovis* or *M. tuberculosis* infection should be a consensus decision between the owner

and the veterinarian, but due to the risk of cat to human transmission and antimicrobial resistance, euthanasia has been proposed by some authorities and experts (http://www.bva.co.uk/News-campaigns-and-policy/Newsroom/News-releases/Updated-statement-on-TB-in-cats/ 2014). Similarly, euthanasia might be considered after infection with any of the other potential zoonotic species (*M. microti* and *M.* avium).

In the recently published outbreaks in cats that might have been infected following the consumption of contaminated raw food, no transmission to owners was observed. However, there is concern about the potential risk of infection to owners by them handling contaminated raw food during meal preparation, as well as home environment contamination by *M. bovis* faecal shedding by the cats.

MAC species, particularly subsp *hominissuis*, are potentially transmissible from cat to humans, but so far there have been no reports of human cases caused by cat infection (Biet et al., 2005).

There is a single published report from Australia of a human mycobacterial infection, a case of *Mycobacterium marinum* (in the NTM group) local skin infection, acquired from a cat after a scratch (Phan and Relic, 2010).

The use of gloves is strongly recommended when treating cats with any suspected mycobacterial infections and/or when taking and processing biopsy samples. In TB-endemic areas, veterinarians and technicians handling cats with compatible lesions should use gloves, facial filtration particle masks and protective clothing. Infections are most likely to be spread (to humans and other susceptible hosts) via discharges from skin wounds or via the respiratory tract if this system is involved (e.g. coughing, collection of bronchoalveolar lavage samples, intubation). The effectiveness of disinfectants against mycobacterial species should be checked as some (e.g. chlorhexidine) are not mycobacteriocidal. A country's regulation should be consulted to determine if any health authorities must be notified if mycobacterial disease (e.g. due to *M. tuberculosis* or *M. bovis*) is confirmed.

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