



Companion Animal Mycobacterial Infections: Treatment Protocol

In the UK, the majority of mycobacterial infections in cats are caused by tuberculous mycobacteria. The only large culture study showed ~35% of infections to be caused by *Mycobacterium microti* (~20%) or *Mycobacterium bovis* (~15%), with ~50% of case submissions failing to grow. The most common non-tuberculous mycobacteria (NTM) are in the *M. avium* complex (MAC), and a wide range of NTM can infect cats.

It is important to consider the factors below before undertaking treatment:

There is a potential zoonotic risk – especially for the species of the tuberculosis (TB) complex group. All members of the affected cat's household must be considered and it is important to determine any potentially immunosuppressed individuals (e.g. people with human immunodeficiency virus or who are undergoing chemotherapy). Treatment should be thoroughly considered where such individuals may be exposed especially if the affected cat has generalized disease, cavitating lesions within the respiratory tract or extensive draining cutaneous lesions as these may increase the risk of transmission.

Treatment is almost always long term – this can be difficult to maintain if the patient is non-compliant, due to the inherent toxicity of some of the drugs and the financial costs involved. In some cases, the drugs may at best suppress disease and indefinite treatment may be required (Sieber-Ruckstuhl *et al.*, 2007; Greene and Gunn-Moore, 2011). Uncomplicated cutaneous cases with or without diffuse pulmonary changes carry the most favourable prognosis where treatment is successful in over 80% of cases.

Placement of a feeding tube may be required to improve compliance with medications.

Interim management – pending a definitive diagnosis, interim therapy with a fluoroquinolone is recommended in cases of localized cutaneous infection.

Pradofloxacin (or moxifloxacin) is recommended as it is more effective against mycobacteria than the older fluoroquinolones, such as marbofloxacin. With more extensive disease, the addition of azithromycin is indicated, pending confirmation, then adding rifampin when TB is confirmed.

Treatment of mycobacterial disease

Previously, anti-tuberculosis treatment was given in an initial and then a continuation phase; however, it is now known that it is better to give all three drugs for 4–6 months, depending on the extent of disease, and always for at least 2 months following complete resolution of the lesions. Extensive clinical experience supports using rifampin, pradofloxacin and azithromycin as a starting point; however, NTM infections may need different combinations.

Table 1: First-line anti-tuberculous medications; a triple combination comprising one of the fluoroquinolones, a macrolide/azalide and rifampicin is frequently used.²⁸⁵

Drug	Uses	Dosing	Effects of toxicity
Pradofloxacin^a	First-line treatment for TB, NTM	3-5mg/kg PO q 24 hrs (doses up to 7.5mg/kg have been reported as safe).	Reversible neutropenia (rare in cats), seizures in cats with pre-existing CNS disease
Rifampicin^b	First-line treatment for TB, NTM	5-10mg/kg PO q 24 hrs by mouth	Side effects in ~20% of cases, with severe side effects in ~5%. Poor palatability, nausea, discoloration of body fluids, generalized erythema and pruritus, hyperaesthesia, CNS signs, hepatotoxicity, anaphylaxis. Teratogenic
Clarithromycin^b	First-line treatment for TB, NTM, FLS, NTM	7-15mg/kg PO q 12 hrs	Possible GI signs
Azithromycin^c	First-line treatment for TB, NTM, FLS, NTM	5-15mg/kg PO q 24 hrs	Possible GI signs
Isoniazid^b	Second-line treatment for TB	10-20mg/kg PO q 24 hrs	Hepatotoxicity, peripheral neuritis, seizures, acute renal failure
Ethambutol^b	Second-line treatment for TB, NTM	10-25mg/kg PO q 24 hrs	Optic neuritis
Pyrazinamide^{b,e}	Second-line treatment for TB	15-40mg/kg PO q 24 hrs	Hepatotoxicity, GI signs
Dihydro-streptomycin^b	Second-line treatment for TB	5mg/kg i.m. q 24hrs	Ototoxicity
Clofazimin^{b,f}	Treatment for FLS, NTM	4-8mg/kg (max 25mg total) PO q 24-48 hrs	Hepatotoxicity, GI signs, discoloration of body fluids, photosensitization, pitting corneal lesions
Doxycycline^g	Second-line treatment for NTM, MAC	5-10mg/kg PO q 12-24 hrs	GI signs, oesophagitis
Amikacin^b	Second-line treatment for NTM, MAC	10-15mg/kg i.v., i.m., s.c. q 24hrs	Nephrotoxic, ototoxic
Cefoxitin	Second-line treatment for NTM, MAC	20-30mg/kg i.v., i.m., s.c. q 6-8hrs	Pain on i.m., s.c., injection

FLS = feline leprosy syndrome
NTM = non-tuberculous mycobacteria

MAC = *M. avium-intracellulare* complex
TB = tuberculosis.

^a Do not use enrofloxacin in the cat if at all avoidable as it has been associated with retinal degeneration.

^b These drugs may cause potentially serious side effects (e.g. hepatotoxicity or nephrotoxicity); it is advisable to monitor use closely, including routine haematology and serum biochemistry two weeks after starting treatment and again following any change in the cat's demeanour.

^c MAC infections can have inducible resistance genes to macrolides, meaning they appear susceptible *in vitro* but are resistant *in vivo*; where possible (limited by GI signs), use higher doses to reduce the risk of resistance.

^d Particularly useful when treating MAC infections.

^e Not effective against *M. bovis* infection.

^f Can be difficult to obtain.

^g Give with food or give water after the medication to avoid oesophageal injury. Alternatively use the monohydrate over hyclate formulations.

Treatment of non-tuberculous mycobacteria (NTM)

At a minimum, use of a fluoroquinolone is suggested while waiting for PCR or culture results. The new fluoroquinolones (e.g. pradofloxacin or moxifloxacin) are recommended as they have an extended spectrum of activity, which includes some NTM, and they are even effective against MAC infections. MAC infections are particularly difficult to treat.

Clarithromycin or azithromycin should be included ideally in combination with rifampin ± another antibiotic according to culture and susceptibility testing, such as doxycycline or, from human studies, ethambutol.

Pyogranulomatous panniculitis usually requires long-term antibiotics prior to considering surgical management such as reconstructive surgery. Non-surgical cases may require double or triple therapy.

Feline leprosy-type infections (feline leprosy syndrome; FLS) can usually be treated with surgical removal of small nodules, which may be curative. Where medical management is needed, clarithromycin, pradofloxacin and rifampin or clofazimine are recommended.

Doxycycline, fluoroquinolones and aminoglycosides may also be useful. Dapsone is considered too toxic for use in cats and is antagonistic to clofazimine. Treatment should be continued until the lesions have completely resolved, and ideally for a further 2–3 months to reduce the risk of recurrence; however, some cases require life-long clarithromycin to prevent recurrence.

Table 2: Susceptibility and resistance of mycobacterial species to potential drugs for the treatment of NTM in cats.

Mycobacterial species	Susceptibility	Generally resistant
<i>M. avium</i>	Clarithromycin, rifampin, doxycycline, ethambutol, pradofloxacin, clofazimine, amikacin Recommended: clarithromycin or azithromycin and rifampin and another drug	Older fluoroquinolones, cefovecin. Potentially inadvisable to give just a new fluoroquinolone and clarithromycin or azithromycin
<i>M. fortuitum</i>	Recommended: pradofloxacin + amikacin (100%), cefoxitin (94%), older fluoroquinolones (75%), clarithromycin (~75%) clofazimine, rifampin, gentamicin or doxycycline (29% ^a)	Trimethoprim ± sulphonamide, cefovecin, clarithromycin
<i>M. smegmatis</i>	Fluoroquinolones, tetracyclines, gentamicin, trimethoprim ± sulphonamide, clofazimine Recommended: pradofloxacin and doxycycline	Clarithromycin, cefovecin
<i>M. chelonae-abscessus</i>	Amikacin (100%), cefoxitin (94%) ciprofloxacin (75%) clarithromycin (71% ^a), pradofloxacin, clofazimine Recommended: azithromycin or clarithromycin and another drug	Many oral medications, including doxycycline and older fluoroquinolones. Do not give pradofloxacin or moxifloxacin with azithromycin or clarithromycin
<i>M. xenopi</i>	Fluoroquinolones, clarithromycin, rifampin, clofazimine	

^a Some studies have shown these drugs to be either more or less active.

Table continued...

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Mycobacterial species	Susceptibility	Generally resistant
<i>M. simiae</i>	Rifampin, clarithromycin, fluoroquinolones, amikacin, clofazimine	
<i>M. thermoresistibile</i>	Rifampin, doxycycline, clarithromycin	
<i>M. terrae</i>	Clarithromycin, azithromycin, ethambutol	
<i>M. genavense</i>	Clarithromycin, fluoroquinolones, ethambutol	

Managing side effects

Cats may suffer side effects while receiving treatment for mycobacterial infections, especially with rifampin. While side effects can be concerning to owners and veterinary professionals, this drug is essential for optimizing the outcome of treating cats with TB and is the only drug in the triple therapy approach with activity against non-replicating bacteria.

To help manage dermatological side effects such as pruritus, anti-histamines can be used, chlorphenamine therapy has been reported but the ideal dose and interval is unknown and efficacy is not established clinically. Focal pruritic lesions can also be managed with topical hydrocortisone aceponate spray.

Hepatotoxicity is another possible side effect of rifampin, which may manifest clinically as hyporexia, nausea or vomiting, or may be identified with increased enzymes on serum biochemistry. S-Adenosylmethionine (SAME) (20 mg/kg p.o. q24h) is one hepatoprotective agent that is widely used in cases of drug-induced liver toxicity, as well as in cases of liver disease.

An intriguing alternative agent is *N*-acetylcysteine (NAC) (600 mg/cat p.o. q12h); while pharmacological data are lacking for its use in cats, it is safe and well tolerated. NAC has an unpleasant taste and smell, so giving whole capsules is usually advised. Nausea and vomiting are potential side effects, and drooling occurs when the capsule content is mixed with too little food. Since NAC can cause bronchial spasm, it should be used with caution in animals with asthma. NAC helps to restore blood glutathione concentrations, and thus antioxidant capacity. It has also been shown to reduce bacterial counts and the severity of lesions.

Restoration of antioxidant capacity helps reduce the toxic side effects of anti-TB drugs such as rifampin and isoniazid, which are mediated by oxidant-driven damage to the liver. Short-term studies have also shown that NAC has some direct anti-mycobacterial activity and can reduce growth of bacteria both *in vitro* and *in vivo*.