Companion Animal Mycobacterial Infections: Treatment and Zoonotic Risks

Standard first line therapy for companion animal mycobacterial infections should comprise a fluoroquinolone, a macrolide/azalide and rifampicin, as detailed in the table below. In feline infections the preferred combination is pradofloxacin, azithyromycin and rifampicin. In dogs it is enrofloxacin, clarithromycin and rifampicin. Treatment needs to continue for two months beyond the resolution of all clinical signs which includes radiographic abnormalities seen at the time of diagnosis. This is why taking thoracic radiographs at the time of diagnosis is so critical. Typically, overall treatment is 3-6 months in duration.

While the introduction of rifampicin is usually withheld until confirmation of TB, it should be started as soon as possible. The best results are gained when all three drugs are given together.

NB **We no longer recommend an Introduction phase of 3 drugs, then a Continuation phase of just 2 of them as this gives a much poorer prognosis. A combination of the three antibiotics should be continued throughout the course of therapy.**

For cats, the fluoroquinolone of choice is pradofloxacin due to its excellent safety profile and its known *in vitro* activity against mycobacteria when compared to older fluoroquinolones. Where this is not available the use of marbofloxacin can be considered. Enrofloxacin is **unacceptable** for use in cats due to its association with acute irreversible retinopathy however is a good first line agent for dogs. The azalide of choice for cats is azithromycin due to a dosage pattern of once every 24 hours which eases adherence to treatment, plus its concentration within pulmonary macrophages. In dogs, clarithromycin is the preferred choice due to the size of tablets available for accurate dosing.

Rifampicin has long been a cornerstone of anti-tuberculosis, and more general anti-mycobacterial medical therapy. Importantly, it has good efficacy against both extracellular mycobacteria as well as those slowly and persistently replicating within macrophages. However, it should **never** be used as a monotherapy for mycobacterial disease as resistance develops rapidly. Rifampicin is known to be a potent inducer of the hepatic cytochrome P450 system and so has the potential to be significantly hepatotoxic when used chronically.

Serum biochemistry should be checked two weeks into treatment or if the patient becomes unwell whilst receiving rifampicin.

Treatment with rifampicin should be stopped if circulating levels of liver enzymes significantly exceed the upper reference interval, hyperbilirubinemia develops, or patients develop clinical signs attributable to hepatic dysfunction. If this occurs treatment should be stopped and once recovered, the rifampicin can be re-introduced at half of the previous dose with close monitoring to ensure the hepatopathy does not recur. Liver support such as SAMe can, anecdotally, be helpful in these cases.

Rifampicin is excreted in all bodily fluids and may cause urine, tears, and saliva to discolour to red-orange in colour. This is not clinically significant, but it can be distressing for clients who are unprepared, especially as there is the potential for the discoloration to be mistaken for haemorrhage. Deposition of the drug within the skin can cause skin discoloration, irritation and, occasionally, hyperesthesia in both cats and dogs.

Rifampicin is a potential teratogen and so should only be handled by owners wearing gloves and should not be administered to pregnant queens.

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

Drug	Product	Dosing	Contraindications	Side Effects
Pradofloxacin	Veraflox™ 25mg/ml suspension or 15mg tablets	3-5mg/kg PO q 24 hours (doses up to 7.5mg/kg have been reported as safe).	Not in dogs <12 months of age (18 months in giant breeds) or cats <6 weeks of age due to potential adverse effects on cartilage. Do not use in animals with epilepsy.	Neutropenia (not clinically significant) with high doses and/or long courses.
Marbofloxacin	Marbocyl™ 20mg tablets	2mg/kg PO q 24 hours	As for pradofloxacin.	Intermittent vomiting and transient diarrhoea on instigation of treatment.
Azithromycin	Zithromax™ 250mg capsule 50mg/ml suspension	5-15mg/kg PO q 24 hours	Pre-existing cardiopathy esp. arrhythmogenic diseases. Pre-existing hepatopathy.	Intermittent vomiting and diarrhoea possible but uncommon.
Clarithromycin	*Generic* 500mg tablet 50mg/ml suspension	7.5mg/kg PO q 12 hours	Concurrent use of NSAIDs or antacids. Pre-existing hepatopathy.	Pinnal erythema. Generalized erythema. Hepatotoxicity.
Rifampicin	Rifadin™ 300mg capsule 20mg/ml suspension	5-10 mg/kg PO q 24 hours by mouth	Pre-existing hepatopathy. **Tetratogenic –** avoid use in pregnant queens. Owners should wear gloves and ideally pregnant people should avoid handling at all.	Hepatotoxicity; induction of liver enzymes, anorexia, generalized erythema and pruritus. CNS[a] signs. Discoloration of body fluids.

PO; *per os* [a] Central nervous system [b] NSAIDs; non-steroidal anti-inflammatory drugs.

Treatment should be given for at least three months and for two months beyond the resolution of clinical signs (including radiographic or ultrasonographic abnormalities), whichever is longer. This means that on average, cases with skin and lymph node involvement typically require three months of treatment whereas those with pulmonary changes as well or other systemic spread usually require upwards of six months to ensure resolution. The prognosis was historically guarded with only 40% of cats reported to respond to treatment. However, with the implementation of the outlined treatment the prognosis has improved to nearly 80% of cats with MTBC infections causing skin lesions and/or lymphadenomegaly, even with secondary pulmonary spread.

The MAC group of organisms are more resistant to treatment, likely due to inherent drug resistance patterns so the prognosis is more guarded with only 50-60% of cases achieving clinical remission and typically with longer courses of treatment (usually at least six months but sometimes in excess of 12 months is needed).

Zoonotic Considerations

Before beginning treatment, it is important to ensure that owners and persons in close contact with the patient are fully informed of, and clearly understand the potential zoonotic risks associated with being in contact with an infected animal. The greatest risk is posed by members of the MTBC of mycobacteria:

- *M. tuberculosis*: Though rare, infection with *M. tuberculosis* would be considered a significant zoonotic risk. Finding an infected canine should trigger a search for a possible infecting human. Infected animals should be euthanased and their bodies cremated (not buried).
- *M. bovis*: Currently, only ~1% of human tuberculosis cases in the UK are caused by *M. bovis* infection. The rare cases of human *M. bovis* TB that have resulted from exposure to cats have occurred where the cats have had skin lesions discharging purulent material containing many organisms. The Health Security Agency consider the risk to humans from *M. bovis* infected pets to be “very low”. That said, the risk is still present and should be considered seriously in the context of humans with specific risk factors for transmission (see below) and the clinical signs present. Extensive and/or purulent lesions pose the greatest risk to human health and are generally less responsive to treatment. By comparison, single non-ulcerated skin lesions and/or regional lymphadenopathy carry very low zoonotic risk and may be very amenable to treatment.
- *M. microti*: The risk to humans of M. microti is significantly lower than that of *M. bovis*. Very few human cases of infection with this organism have ever been reported and none have been shown to have resulted from exposure to an infected cat or dog.
- *MAC*: Whilst not members of the MTBC, this group of organisms can infect humans in the presence of specific risk factors (see below) – again, none have been shown to have resulted from exposure to an infected companion animal.

The following list of risk factors has been compiled from advice published by public health organisations from across the UK and WHO guidelines. Humans are considered at heightened risk if they:

- are under five years old (some sources suggest 12 years)
- are pregnant
- are HIV-positive
- suffer from substance misuse
- have been diagnosed with diabetes mellitus
- suffer (severe) kidney disease
- have ever received a solid organ transplant
- are a cancer patient receiving chemotherapy or radiation therapy
- have any medical condition requiring treatment with systemic corticosteroids
- require specialized treatment for rheumatoid arthritis or Crohn's disease
- are receiving tumour necrosis factor alpha (TNF-α) inhibitors.

In any of the above situations, owners and veterinarians are strongly discouraged away from animal treatment.