Antifungal agents of use in animal health – Practical applications

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Antifungal agents of use in animal health – practical applications

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The purpose of this paper is to provide an overview of antifungal agents currently in use in veterinary medicine. The practical applications and the therapeutic regimens that have proved successful in the treatment and prevention of fungal infections in dogs and cats, cattle and sheep, horse, pig, poultry and other birds, rodents, rabbits and fur animals are summarized.

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INTRODUCTION

Of the almost 70 000 species of fungi that have been recognized and described, fewer than 100 fungal species approach the status of regular human pathogens (Odds, 1996). About 50 of these species are also pathogenic for animals and some 70 species, such as *Saprolegnia* in fish or *Ascosphaera* in bees, cause disease in animals only.

Compared with mycoses in humans, mycotic diseases in animals have received much less attention. This is surprising as dermatophytes are the oldest known agents of infectious diseases in animals. They are responsible for a significant number of zoonotic infections: in rural areas, up to 80% of fungal infections of human skin may be of animal origin, and in an urban environment, 20% of such human infections can be the result of close contact with dogs and cats (Richard *et al*., 1994). Perhaps the first report of ringworm as a zoonosis is that of a veterinary surgeon who in 1820 noted the infection of a Swiss girl from cattle (described by Smith *et al*., 1992). Ringworm of cattle is nearly exclusively caused by *Trichophyton verrucosum*. This skin disease is present world-wide and is responsible for high economic losses in cattle farming (Weber, 2000). Infections in humans result from a direct contact with cattle or infected fomites. Dermatophytosis in sheep is considered to be a rare disease; *T. verrucosum* and *T. mentagrophytes* var. *mentagrophytes* have been the major agents encountered (Pier *et al*., 1994). Other zoophilic dermatophytes and their common hosts are: *T. equinum* (horse), *T. mentagrophytes* var. *mentagrophytes* (rodent, humans), *T. mentagrophytes* var. *quinckeanum* (mouse), *T. mentagrophytes* var. *erinacei* (hedgehog, humans), *T. simii* (primate, birds), *Microsporum canis* (cat, dog, primate, humans), *M. equinum* (horse), *M. gallinae* (chickens and other fowl), *M. nanum* (pig) and *M. persicolor* (vole) (Pier *et al*., 1994; Pier & Moriello, 1998).

In addition to dermatophytes many other fungi and yeasts are described as agents of animal and human disease. In 1873, S. Rivolta presented evidence that a disease of equines, known as epizootic lymphangitis (farcy), was caused by a yeast-like species, now known as *Histoplasma farciminosum* (*H. capsulatum* var. *farciminosum*) (see Ajello, 1998). Epizootic lymphangitis is now a relatively rare infectious disease of horses in certain parts of the world, such as the Mediterranean area and East Africa (al-Ani, 1999). Another dimorphic fungus, *Sporothrix schenckii*, has been isolated from skin lesions and nails of cats (Schubach *et al*., 2001). Oral and oesophageal lesions involving *Candida albicans* have been demonstrated in birds, piglets and calves. Another important pathogen of piglets is *C. slooffiae* (Smith *et al*., 1992).

The nonlipid-dependent *Malassezia* species, *M. pachydermatis*, identified by Dufait (1985) as a possible cause of seborrheoic dermatitis in dogs, is frequently recovered from wild and domestic carnivores including cats, bears, pinnipeds, ferrets and foxes. It has also been isolated from horses, pigs and birds (Dufait, 1985; Pier *et al*., 2000). The lipid-dependent *Malassezia* yeasts appear more anthropophilic, but, *M. slooffiae* may be isolated from pigs, *M. globosa* from cats and cattle, *M. sympodialis* from cats, and *M. furfur* from the skin and feathers of birds (Pier *et al*., 2000).

Yeast infections of the mammary glands are responsible for 2–3% of clinical mastitis. Mycotic disorders of the udder are caused by yeasts belonging to several genera (*Candida*, *Rhodotorula, Trichosporon*) (Richard *et al*., 1994; Lagneau *et al*., 1996; Krukowski *et al*., 2001). *Aspergillus fumigatus* and *A. nidulans* have also been described as causal agents of bovine mastitis (Schallibaum *et al*., 1980). *Aspergillus fumigatus* and the zygomycete *Mortierella wolfii* are important agents of abortion in cattle (reviewed by Smith *et al*., 1992). In poultry (e.g. brooder pneumonia in day-old chicks) and captive/stressed water birds outbreaks of aspergillosis can be explosive with high mortality (Richard *et al*., 1994). Fungal infections of the nasal cavity are a common cause of nasal disease in the dog, cat and horse. *Aspergillus fumigatus* most commonly affects dogs; *Cryptococcus neoformans* is the most common fungus isolated from the cat (Wolf, 1992). *Exophiala*, *Alternaria*, *Trichosporon*, *Blastomyces* and *Histoplasma* occasionally cause nasal disease in dogs and cats (Wolf, 1992).

Rhinosporidium seeberi is associated with tumour-like epithelial proliferations in the nasal cavity of humans, dogs, cats, horses, cattle and a number of avian species (see Wallin *et al*., 2001).

Pythiosis is a cosmopolitan granulomatous disease caused by an aquatic fungus *Pythium insidiosum*. The disease affects horses, cattle, dogs, cats and humans (Thianprasit *et al.*, 1996; Pier *et al.*, 2000). The equine species is the most commonly affected. Treatment of infections caused by *P. insidiosum* in animals and human beings is difficult. The usual treatment for equine pythiosis is surgical removal.

For most of the other mycoses, practitioners have a variety of antifungal agents at their disposal (see review 'Antifungal agents of use in animal health – Chemical, biochemical and pharmacological aspects' in the previous number of this Journal).

DOGS AND CATS

The most common condition caused by fungi in the western world in dogs and cats is dermatophytosis. The three main species involved are *M. canis*, *M. gypseum* and *T. mentagrophytes*. Reported incidence rates of dermatophytosis range between 5 and 20%. In the dog, *M. canis* is found in 70%, *Trichophyton* in 20% and *M. gypseum* in 10% of the cases. In cats, 98% of the cases of dermatophytosis is caused by *M. canis*. *Microsporum gypseum* and *Trichophyton* infections are rare in cats. *Microsporum* lesions in dogs are typically circular with hair loss and broken hairs at the periphery, in some cases also with crusts. In cats, *Microsporum* lesions can be present under many different forms. *Trichophyton* lesions generally cause more inflammation and may contain intact hairs.

Although dermatophyte infections have a limited impact on the general health condition of the animal, they are of importance especially from a zoonotic point of view.

Strategic management of dermatophytosis always includes (systemic or topical) treatment of the animal and environmental decontamination.

Superficial mycoses can also be caused by yeasts (*Candida* or *Malassezia*). *Malassezia* dermatitis is an increasingly recognized dermatosis in dogs and is commonly associated with an underlying cause, such as atopy or seborrhoea. Certain dog breeds appear to be predisposed. Pruritus and erythema are typical clinical signs. In cats, *Malassezia* dermatitis is rarely reported. *Malassezia pachydermatis* has been demonstrated to contribute to the aetiology of otitis externa in dogs and cats (Crespo *et al.*, 2002). Candidosis is a rare disease in dogs and cats (Scott *et al.*, 1995). Predilection sites are mucous membranes, the skin or the gastrointestinal tract.

Canine nasal aspergillosis is a localized fungal infection that occurs in the sinuses and the nasal cavity. It is caused by *Aspergillus fumigatus* and/or other *Aspergillus* spp.

Deep mycoses or generalized mycoses (e.g. cryptococcosis, blastomycosis, histoplasmosis, coccidioidomycosis, sporotrichosis) are uncommon to rare in the western world but their incidence in tropical areas may be high. In some cases, they can be life-threatening.

Whereas treatment of dermatophytosis in dogs can generally be achieved with topical treatment alone, cats usually require systemic treatment. Strategic treatment of dermatophytosis in dogs and cats should always include environmental decontamination, which prevents spread of infection to other animals or humans and re-infection after the end of treatment of the animal. Clipping of the haircoat may be recommended, especially in long-haired breeds. One of the classical mistakes made in the treatment of fungal infections is termination of treatment at the time when clinical cure is observed. As clinical cure always precedes mycological cure, this will often lead to a relapse.

AZOLE ANTIFUNGALS

Ketoconazole

Dog

Systemic (oral) use. Ketoconazole is licensed for dogs only in France (Ketofungol®; Janssen, Beerse, Belgium). In other countries, off-label use of the human product (Nizoral®; Janssen) is quite common. Ketoconazole is highly effective in the treatment of canine dermatophytosis (De Keyser & Van den Brande, 1983; Angarano & Scott, 1987).

The dose for treatment of dermatophytosis is 10 mg/kg/day for 3–4 weeks. Tablets should be given with a meal, in order to obtain maximal absorption.

Higher doses of oral ketoconazole were shown to be effective for treatment of systemic cryptococcosis (Noxon *et al.*, 1986; Mason *et al.*, 1989) and coccidioidomycosis (Hinsch, 1988). Ketoconazole is also used for treatment of *Malassezia* dermatitis in dogs. Treatment at 5–10 mg/kg/day for 3 weeks appeared to be highly effective (Bensignor, 2001). Ketoconazole is effective for treatment of *Candida* infections at 10 mg/kg for 6–8 weeks (Moriello, 1986).

Topical use. The human shampoo formulation (Nizoral® shampoo, Janssen; containing 2% ketoconazole) is not licensed for use in dogs, but is also quite commonly used and highly effective for treatment of dermatophytosis or *Malassezia* infections (Carlotti, 2001).

Ketoconazole ointment and cream (Nizoral®; Janssen) are occasionally used for topical application on small dermatophytosis lesions.

Cat

Systemic use. Ketoconazole is not licensed for cats. Nevertheless, it is quite commonly used and effective for treatment of dermatophytosis (De Keyser & Van Den Brande, 1983; Woodard, 1983). The oral dose is similar as in dogs (10 mg/kg/day). Treatment duration may vary between 2 and 10 weeks (Medleau & White-Wheiters, 1992; Medleau & Chalmers, 1992). As in dogs, ketoconazole should be given together with food in order to obtain an optimal absorption.

Ketoconazole also appears effective for treatment of *Malassezia* (Godfrey, 1998), cryptococcosis (Legendre *et al.*, 1982; Schulman, 1985; Noxon *et al.*, 1986), histoplasmosis (Noxon *et al.*, 1982) and *Sporothrix schenckii* (Nakamura *et al.*, 1995).

Topical use. Topical ketoconazole formulations (shampoo, cream, ointment) are also used in cats.

However, most of the dermatophytosis cases in cats require systemic treatment.

Enilconazole

Dog

Enilconazole is licensed for topical use in dogs. It is available as a 10% concentrated solution (Imaverol®; Janssen), to be diluted 1/50 in tap water to yield a 0.2% solution. Treatment consists of four whole-body applications with 3–4-day intervals. The product is highly effective against dermatophytes (*Microsporum* spp. and *Trichophyton* spp.) (Desplenter, 1989; White-Wheithers & Medleau *et al.*, 1995) and also against *Malassezia* (Marouteix, 1994; Carlotti 2001).

Enilconazole is also used for sinus irrigation in dogs with nasal aspergillosis (Lanthier & Chalifoux, 1991; Oosterhout & Venker-van Haagen, 1991; Sharp *et al.*, 1993; McCullough *et al.*, 1998).

Cat

Although not licensed for cats (except in France), enilconazole is being used for topical treatment of dermatophytosis at a treatment schedule identical to that in dogs (Bussieras *et al.*, 1984; Carlotti & Couprie, 1988; Desplenter, 1989; de Jaham & Paradis, 1997). Topical enilconazole appears to be well-tolerated by cats (de Jaham *et al.*, 1996; Hnilica *et al.*, 2000).

Environment

Enilconazole is available in special formulations for decontamination of the environment – as part of a strategic programme.

Both a smoke generator (5 g enilconazole; for a 50-m^3 room) and a 15% emulsifiable concentrate (to be diluted 1/100 in tap water; can be nebulized or sprayed) are available (Clinafarm® smoke, Clinafarm® spray; Janssen). These formulations are highly effective against spores of dermatophytes (Desplenter, 1989; White-Wheithers & Medleau *et al.*, 1995) and *Aspergillus* spp. (Desplenter, 1988; Van Cutsem *et al.*, 1988).

Itraconazole

Dog

Oral itraconazole is effective for treatment of dermatophytosis in dogs at doses of 10–20 mg/kg daily or with 48-h intervals (Scott *et al.*, 1995).

Doses of 5 mg/kg/day have been demonstrated to be effective for treatment of canine blastomycosis (Legendre *et al.*, 1995), while itraconazole at 7.3 mg/kg/day for 35 days appeared effective for treatment of sporotrichosis (Sykes *et al.*, 2001).

Itraconazole at a dose of 10 mg/kg/day for 2 months following surgery was effective in the treatment of canine nasal aspergillosis (Guaguere *et al.*, 1999).

Cat

Itraconazole is not licensed for use in cats. Nevertheless, the human formulations (Sporanox® 100 mg capsules and 10 mg/mL oral solution; Janssen) are used for treatment of dermatophytosis. The dose of itraconazole for treatment of feline dermatophytosis suggested in the literature is 10 mg/kg/day (Moriello & DeBoer, 1994, 1995a,b). It is recommended to continue treatment until mycological cure (Moriello & DeBoer, 1995a,b).

In an uncontrolled clinical trial, lower doses of itraconazole (1.5–3 mg/kg/day for 15 days) were effective in eight of 15 cats (Mancianti *et al.*, 1998).

The pharmacokinetic characteristics of itraconazole and its persistence in keratin-containing tissues (skin, nails and hairs) allow 'pulse therapy' schedules: an alternate week treatment schedule (5 mg/kg/day for three alternate weeks) is effective (Janssen Animal Health, data on file). A combined continuous/pulse therapy has also been demonstrated to be effective (Colombo *et al.*, 2001).

In a cat infected with *Fonsecaea pedrosi*: two treatment cycles with itraconazole (5 mg/kg given twice daily) induced complete clinical remission, but relapses occurred (Fondati *et al.*, 2001).

Long-term oral itraconazole (5 mg/kg once or twice daily) is effective for treatment of feline cryptococcosis (Medleau *et al.*, 1990, 1995; Kano *et al.*, 1997) and histoplasmosis (Hodges *et al.*, 1994).

Miconazole

Dog–cat

Miconazole is licensed for use in dogs and cats and is included in an otic preparation for treatment of otitis externa (combination with polymyxin B and prednisolone; Surolan®; Janssen). Besides its activity against *Malassezia* spp., miconazole also has activity against Gram-positive bacteria. Moreover, miconazole and polymyxin B appear to have a synergistic effect (Cornelissen & Vanden Bossche, 1983). In several countries, this product is also licensed for local treatment of bacterial or fungal dermatitis.

A shampoo containing 2% miconazole + 2% chlorhexidine (Malaseb®; Leo, Ballerup, Denmark) has been demonstrated to be effective against *Malassezia* (Lloyd & Lamport, 2000). It is also effective as topical adjuvant on top of oral griseofulvin for treatment of dermatophytosis (Paterson *et al.*, 1996; Mason *et al.*, 2000; Sparkes *et al.*, 2000).

Other topical human formulations (Daktarin®, Janssen) can be used for local treatment.

Clotrimazole

Like miconazole, clotrimazole also has some activity against Gram-positive bacteria. It is commonly used in otitis products for dogs and cats (in combination with an antibiotic and an anti-inflammatory agent; Otomax®; Schering-Plough, Union, NJ, USA).

Topical application of clotrimazole has been demonstrated to be effective for treatment of localized dermatophytosis lesions in dogs (McCurdy *et al.*, 1981).

Intranasal infusion of clotrimazole is an effective treatment for canine nasal aspergillosis (Mathews *et al.*, 1998; Smith *et al.*, 1998).

Econazole

Econazole is another azole antifungal that is available in topical formulations only (Pevaryl®, Janssen-Cilag, Beerse, Belgium; available in cream, lotion, powder, spray). The product is not licensed for use in animal health. Its spectrum of activity is comparable with that of miconazole (Heel *et al.*, 1978).

The different formulations can be used for topical treatment of dermatophytosis or *Malassezia* infections.

Fluconazole

Fluconazole (Diflucan®; Pfizer, New York, NY, USA) is not licensed for use in dogs or cats.

Dog

Fluconazole at oral doses of 2.5–5 mg/kg is effective for treatment of canine nasal aspergillosis (Sharp *et al.*, 1991) although the success rate was lower compared with topical enilconazole.

One study described the use of fluconazole for treatment of canine central nervous system cryptococcosis (Tiches *et al.*, 1998). Fluconazole can also be used for treatment of canine blastomycosis (Hill *et al.*, 1995).

Cat

Fluconazole has been successfully used for treatment of cryptococcosis in cats at a dose of 50 mg per cat twice daily (Malik *et al.*, 1992). Lower doses were effective in some cases.

ALLYLAMINES

Terbinafine

Terbinafine (Lamisil®; Novartis, Basel, Switzerland) is not licensed for use in dogs or cats.

There are only limited data available on the use of terbinafine in dogs and cats.

In a study in cats, doses of 30–40 mg/kg once daily were required for treatment of *M. canis* dermatophytosis. Lower doses (10–20 mg/kg) were not different from the untreated control group (Kotnik *et al.*, 2001).

Mancianti *et al.* (1999) treated cats infected with *M. canis* orally once daily with 30 mg/kg of terbinafine over a 2-week period. Three months after the last administration of the drug, 11 of the 12 cats treated showed a complete cure.

In another study, low doses of terbinafine (8.25 mg/kg/day for 21 days) were effective for eradication of *M. canis* spores from the haircoat of asymptomatic carrier cats (Castanon-Olivares *et al.*, 2001).

Terbinafine has a poor activity against yeasts (Balfour & Faulds, 1992) and is not effective for treatment of deep mycoses (Hill *et al.*, 1995).

POLYENES

Amphotericin B

Amphotericin B is not licensed for veterinary use.

Amphotericin B should be administered intravenously because it is not absorbed from the gastrointestinal tract. Moreover, the use of this drug requires intensive patient monitoring because of the risk for adverse effects (nephrotoxicity). This makes treatment regimens with Amphotericin B costly, labour intensive and risky.

It is effective for treatment of blastomycosis, histoplasmosis, coccidioidomycosis, cryptococcosis and candidosis (Hill *et al.*, 1995).

Sometimes amphotericin B is used in conjunction with an azole antifungal.

Nystatin

Nystatin is licensed for use in dogs and cats as an ingredient in otic preparations (Fucidin® or Canaural®, Leo Pharmaceuticals; Panolog®, Fort Dodge, Overland Park, KS, USA; Oridermyl®, Vetoquinol, Lure, France) or cream (Panolog® cream, Fort Dodge).

The cream is used for treatment of dermatoses in dogs and cats (Nesbitt & Fox, 1981).

Nystatin is active against *Candida* (Lorenzini & De Bernardis, 1986).

Natamycin

Natamycin is licensed for veterinary use (Mycophyt®, Intervet, Boxmeer, The Netherlands) but only for cattle and horses. It is available as powder, which needs to be suspended in water.

Natamycin has a moderate activity against dermatophytes, yeasts and *Aspergillus*.

It can also be used for environmental decontamination.

GRISEOFULVIN

Dog

Griseofulvin is licensed for treatment of dermatophytosis in dogs and is widely used. It is available in tablets (Fulcin®, Leo, various other tradenames). The administration depends on the size component of the active substance (microsize or ultramicrosize). Microsize griseofulvin should be given at a dose of 50 mg/kg once daily or 25 mg/kg twice daily; the dose of ultramicrosize griseofulvin is 5–10 mg/kg once daily (Medleau & White-Wheiters, 1992).

Griseofulvin should be administered with a fatty meal to increase absorption.

Griseofulvin is not active against yeasts (*Malassezia* and *Candida*).

Because of its teratogenic potential, the use of griseofulvin is contraindicated in pregnant animals.

Cat

Griseofulvin is licensed for treatment of dermatophytosis in cats. It is available in tablets (Fulcin®, Leo, various other tradenames).

Griseofulvin is widely used in cats. Doses depend on the quality of the active component (see dog). Griseofulvin is poorly absorbed and should be administered with a fatty meal to increase absorption.

Griseofulvin is effective for treatment of dermatophytosis in cats (Moriello & DeBoer, 1994, 1995a).

The onset of activity of griseofulvin is slow. It has been demonstrated that oral griseofulvin in combination with a miconazole and chlorhexidine shampoo provides better efficacy than griseofulvin alone (Sparkes *et al*., 2000).

Griseofulvin is not active against yeasts (*Malassezia* and *Candida*).

Because of its teratogenic potential, griseofulvin should not be used during pregnancy (Scott *et al*., 1975).

THIABENDAZOLE

Thiabendazole is licensed for use in dogs and cats as ingredient of an otic preparation (Tresaderm®, Merial Duluth, GA, USA – contains thiabendazole + neomycin + dexamethasone).

LUFENURON

Lufenuron is a chitin synthetase inhibitor and is registered for prevention and control of flea infestations in dogs and cats (Program, Novartis).

Recently, lufenuron has been put forward as an effective treatment for dermatophytosis in dogs and cats. A study indicated good efficacy at a single oral dose of 54–68.3 mg/kg orally in dogs and 51.2–266 mg/kg in cats (Ben-Ziony & Arzi, 2000). This publication was followed by letters to the editor with revised dosage recommendations of at least 80 mg/kg orally with a second dose after 2 weeks (Ben-Ziony & Arzi, 2001) and 80–100 mg/kg orally to be repeated biweekly until culture negative (Ben-Ziony & Arzi, 2002).

However, recent studies indicated that lufenuron at monthly doses of 30 or 133 mg/kg was unable to prevent dermatophyte infection by direct topical challenge (Moriello & Deboer, 2002) and oral doses of 100–140 mg/kg orally did not prevent dermatophyte infection by exposure to experimentally infected cats (Deboer & Moriello, 2002).

A recent study in cattery cats (Guillot *et al*., 2002) evaluated the efficacy of oral lufenuron at 60 mg/kg orally (twice with 30 days interval) in combination with topical enilconazole (weekly rinses during 4 weeks). Although there was a clear reduction in number of cats with clinical lesions and the mean number of fungal cultures was greatly reduced, this schedule did not provide a quick method for management of dermatophytosis in catteries with high infection pressure as clinical cure usually occurred only after several weeks, some of the cats remained culture positive and relapses were observed.

CATTLE AND SHEEP

The main fungal infections in domestic ruminants are dermatophytoses or ringworm, mycotic abortions and mycotic mastitis. Ringworm is nearly exclusively caused by *T. verrucosum*, sometimes by *T. mentagrophytes* and in rare cases by *M. canis*. It is rather rare in sheep and occurs only exceptionally in goats. These dermatophytes develop in the superficial layer of the stratum corneum, in the claws and in the hairs. This skin disease is present world-wide in cattle and can cause high economic losses in cattle farming. Dermatophytes are also responsible for severe skin diseases in humans.

Modern housing conditions with greater density of animals per unit area, and calves kept in loose housing conditions with more physical contact with other animals, carry higher risk of infections. In an Italian study, 19% of the cattle in intense beef breeding and only 4.5% in intense dairy farms and 8% in traditional farms were positive for ringworm (Moretti *et al*., 1998).

In case of highly contagious disease like ringworm, the whole herd may be affected. Therefore, ringworm should be regarded as a 'herd disease' and must be treated accordingly. Treatment of only the clinically affected animals is less-effective than treatment of the complete group (Oldenkamp & Spanoghe, 1977).

It is known that spontaneous recovery from *T. verrucosum* is the rule and reinfection is uncommon. Normally, the disease in individual animals lasts for about 8 weeks and each lesion has a mean duration of about 4 weeks (Edwardson & Andrews, 1979). However, to control the infection, and to reduce the risk of transmission to humans, herd therapy is required.

Since 1979 a Russian live vaccine (LFT 130) and later on a Czechoslovakian live vaccine against bovine ringworm has been used. Effective control of ringworm has been achieved in regions implementing systemic vaccination. In Scandinavian countries vaccination programmes against ringworm are included as a preventative measure to improve the hide quality (Bredahl & Gyllensvaan, 2000). But one needs a booster vaccination for life-long protection and the efficiency is variable. In some herds, some of the calves develop ringworm in spite of early vaccination, mostly in the period between two injections (Naess & Sandvik, 1981; Gudding & Lund, 1995; Kielstein *et al*., 1998; Rybnikar *et al*., 1998).

Treatment of ringworm in cattle (Table 1) with older antimycotic products like thiabendazole, iodine, etisazol and thiadiazine is now quite uncommon. According to the European Consultation Conference on the availability of veterinary medicinal

Table 1. Antifungal drugs in use * in cattle

Antifungal (trade name)	Formulations	Indications	Treatment schedule
Enilconazole			
Imaverol®	Emulsifiable solution	*Trichophyton, Microsporum*	Wash or spray with diluted emulsion (2000 p.p.m.) four times at 3–4-day intervals
Clinafarm®	Antimycotic disinfectant		For disinfecting of environment with spray or smoke generator
Griseofulvin (Fulcin®, Grisovin®)	7.5% powder feed additive	*Trichophyton*	10 mg/kg body weight for 7 days in mild infections; in severe cases 2–3 weeks
Natamycin (Mycophyt®)	Suspension	*Trichophyton, Microsporum*	Spray suspension two times with interval of 4–5 days; retreat remaining lesions after 14 days
Thiadiazine (Defungit®)	Powder for dilution	*Trichophyton, Microsporum*	0.5% Dilution repeat two to three times with interval of 2–4 days; if no bensuldazin cure, repeat schedule after 14 days
Thiabendazole (in 90% DMSO)	4% Solution, ointment	*Trichophyton, Microsporum*	Washing with solution

*Drugs in bold are officially licensed as veterinary products for cattle in most of the EEC countries.
DMSO, dimethyl sulphoxide.

products only two substances – enilconazole and natamycin – will be left to treat ringworm. The in-feed medication of griseofulvin is no longer licensed for food producing animals in the European Economic Community.

Dermatophytoses

Trichophyton verrucosum has a long incubation period and the spores remain viable for many months. Practically every infected stable has asymptomatic spore carriers. Effective control is based on repeated topical treatment of all the animals from an infected stable, preferably together with a thorough antimycotic disinfection of the entire stable and all the materials with which the animals come into contact, such as halters, milking equipment, fences, cleaning materials and stalls.

Thiabendazole

The anthelmintic thiabendazole has some antimycotic activity against *T. verrucosum*. It can be used topically as an ointment or a solution and is moderately effective after oral administration. In two trials 30–150 g thiabendazole pellets were given for 10 days: i.e. 20–50 mg thiabendazole/kg body weight. Three to 6 weeks later a significant clinical improvement was noted (Schröder & Bernhard, 1979).

Calves infected with ringworm were treated locally with thiabendazole three times 3 days apart. Within 7 days after the last treatment all treated calves were clinically improved, whereas the controls were not. The lesions did not recur in the treated animals during the 6-month period after the last treatment (Khanna *et al.*, 1974).

In three groups of 30 Friesian cattle naturally infected with *T. verrucosum*, one group was treated with 3.75% thiabendazole in glycerine, another with 5% tincture of iodine and the last served as the control group without any treatment. Both the preparations were applied locally on the ringworm lesions at 3-day intervals with a total of four applications. The percentage of animals cured was 86.7 by thiabendazole and 46.7 by tincture of iodine. No recrudescence was observed during the subsequent 4-month period (Pandey, 1979).

In a study on the use of thiabendazole in the treatment of bovine dermatophytosis caused by *T. verrucosum*, 15 infected animals were included. Ten animals were treated with a thiabendazole–dimethyl sulphoxide (DMSO)–salicylic acid mixture and five animals were left untreated as controls. The thiabendazole mixture was used topically on the skin lesions. Lesions resolved after 12 applications and 80% of the treated animals proved negative on mycological examination. All lesions healed completely after 16 applications (Gabal, 1986).

Griseofulvin

Griseofulvin influences the division of the cell nucleus and inhibits mitosis. Therefore it is not given to breeding or pregnant animals. Since 1997 in-feed medication of griseofulvin is no longer licensed for cattle in the EEC.

In cattle griseofulvin can be used orally as a powder or as granules mixed into the feed. The producers of griseofulvin recommended daily doses of 10–50 mg/kg during 1–3 weeks for ringworm. It is important that treatment is continued at least 1 week after disappearance of clinical signs. Griseofulvin inhibits growth of various dermatophytes but is ineffective against other fungi. In his review of antifungal agents, Huber (1991) stated that the doses of griseofulvin that produce beneficial therapeutic or preventive effect in cattle range from 10 to 30 mg/kg during at least 7–35 days. All these treatment schedules are expensive therapies so that they are mainly used in severe and recurrent cases.

A treatment schedule of 1 week with doses lower than 10 mg/kg gives incomplete results. In a trial, 40 cattle between 150 and 500 kg suffering from trichophytosis received 7.5 mg/kg in the feed for 7 days. The following results were obtained 4 weeks after the last treatment: complete healing had occurred in 83% of the animals and 15% had incomplete healing (Reuss, 1978).

Treatment of 10 ringworm-infected calves on the farm was undertaken with the daily administration of griseofulvin powder for 7 days at a rate of 7.5 mg/kg body weight and compared with nine infected control calves. The treated group showed fewer new lesions than the control group and less new lesions per infected animal. But the appearance of the last new lesions was earlier in the treated group than in the control group. The duration of infection in the former treated and control group was 49 and 98 days, respectively (Andrews & Edwardson, 1981).

In Ireland, an excellent response was obtained with griseofulvin at a dose of 7.5 mg/kg for 7 days, in two infected flocks of sheep, after an outbreak of ringworm (Power & Malone, 1987).

Natamycin

Natamycin has moderate activity against dermatophytes, yeasts and *Aspergillus*. It is a powder for preparation of a suspension containing 0.1% natamycin for topical use after reconstitution with water. For cattle it is applied by spraying or sponging. Its toxicity is very low and it is not absorbed through the skin (Raab, 1972).

In an extensive trial four different formulations of natamycin were tested on 1689 cattle (30 farms) infected with ringworm. Under various field conditions spraying of the highest dose of natamycin S-200 was effective, even in severe infections. Fifty per cent was completely cured and another 42% showed clinical improvement (Oldenkamp & Kommerij, 1976).

Treatment with natamycin, two times with 4–5-day interval, as a total body spray on 41 calves, which were naturally infected with *T. verrucosum,* was evaluated with mycological and clinical observations. Ten other infected animals were not treated and considered as control animals. Five to 6 weeks after treatment, 88% had recovered or showed distinct improvement. After 11–12 weeks, 95% of the treated animals had recovered and 91% had a negative culture. All controls yielded a positive culture during the whole observation period (Spanoghe & Oldenkamp, 1977).

Two treatments with natamycin-Spray of 136 cattle given only to animals with visible lesions was less effective than treatment of the complete group (Oldenkamp & Spanoghe, 1977).

In the UK, a total of 258 cattle clinically affected with *T. verrucosum* were treated twice by spraying with a suspension containing natamycin. At 8 weeks after the last treatment, 93% of the affected animals had completely recovered and the remaining 7% had improved markedly; 70% of the mycologically examined animals proved negative at the same time. No re-infection of the recovered animals or spread of the disease was seen up to 6 months after treatment (Oldenkamp, 1988).

Cows naturally infected with *T. verrucosum* from 10 different locations in Germany were treated with natamycin. The cows received twice a whole body spray (0.1%) treatment in an interval of 3 days. Six weeks after treatment, 77.1% of the group could be considered clinically cured (Schulz, 1984).

Enilconazole

Low enilconazole concentrations (1 μg/mL) completely inhibit the growth of the main dermatophytes *Trichophyton* and *Microsporum* and of other moulds such as *Aspergillus*. The formulated product (Imaverol®) is a 10% concentrated solution which is first diluted with 50 times its volume of lukewarm water to give a 2000 p.p.m. ready-to-use solution. A second formulation of 15% enilconazole with different carriers (Clinafarm®) is a specific fungicidal disinfectant for all kinds of animals' living quarters, such as stables, kennels and riding schools, and for the equipment used in these environments.

A total of 234 cattle from 28 different herds with typical ringworm lesions which, after direct examination and culture, were found to be caused by *T. verrucosum*. The animals were subdivided into two groups (165 = A; 69 = B) and treated with enilconazole base, 10% emulsifiable concentrate, diluted in 50 parts of water to produce a 0.2% spray. Group A was treated four times with a spray at weekly intervals. Initially, group B was treated manually with a sponge and with the 0.2% spray, then three times only with the spray. Treatment in group B was carried out at 3–4-day intervals and the total period of treatment was 2 weeks. Enilconazole was very effective. A stereotype positive evolution of the lesions was observed in the majority of cases resulting in stabilization of the lesions, improvement and, finally, the start of new hair growth. Two weeks after the last treatment, 92 and 87% was completely cured in group A and B, respectively. Within 5 weeks, cure rates were 93 and 88%. Topical use of enilconazole as a spray is completely safe for cattle (De Keyser, 1981). Although ringworm occurs mostly in young animals, the product can also be used in lactating cattle. There is no withdrawal time for meat.

The efficacy of enilconazole was evaluated in a problem herd with 12 seriously affected calves and compared with a control group. The animals were sprayed with the 0.2% solution four times with 3-day intervals. One month after the last treatment, all the animals were cured as assessed by clinical and mycological evaluation (Schepens & Spanoghe, 1981).

A total of 537 cattle of different age and breeds from different types of stables were involved in eight clinical trials. Diagnosis was based on clinical examination, or after direct microscopic examination, or after culture of scrapings. The animals were treated four times with 3–4-day intertreatment intervals. Treatment was performed with a sponge and a knapsack sprayer or a high pressure sprayer. A volume of 0.5 L for a calf to 1 L of the diluted product was used per animal and per application. The treatment, evaluated on clinical parameters, was very effective: 93.7% was completely cured (M. Engelen & L. Desplenter, unpublished results).

Mycotic mastitis

Yeast infections of the mammary glands are responsible for 2–3% of clinical mastitis. Mycotic disorders of the udder are caused by yeasts belonging to several genera (*Candida, Cryptococcus* or *Trichosporon*) and by other microorganisms that may be part of the normal flora of the skin, udder and teats, or part of the saprophytic flora of the surroundings. In over three quarters of cases, the cause of bovine mycotic mastitis are *Candida* species such as *C. albicans, C. glabrata, C. kefyr, C. tropicalis, C. krusei, C. parapsilosis*. Most of them are able to grow at 40 °C (Lagneau *et al*., 1996). Historically, mastitis caused by yeast has been treated by frequent stripping of the affected quarter.

Antimycotic drugs could be supportive, but according to van Veen and Kremer (1992) there is no clear evidence of the effectiveness of this therapy.

In vitro antimycotic sensitivity of yeasts isolated from infected bovine mammary glands was studied in 91 yeast cultures. These cultures were most sensitive to clotrimazole followed by ketoconazole, nystatin, miconazole and amphotericin B and least sensitive to 5-fluorocystine. The most sensitive yeast was *C. lusitaniae* (85.7%) and the least sensitive was *C. rugosa* (31.9%) (McDonald *et al*., 1980).

Two groups of cows with mastitis caused by *Candida* spp., *Prototheca zopfii* and *Trichosporon* spp. were treated with thiabendazole and miconazole. Miconazole for infusion was prepared by diluting 50 or 100 mg of Monistat i.v. to 60 mL of solution with sterile water. They were given 45 g of thiabendazole p.o. daily for 3 days. Miconazole was infused aseptically into affected quarters of the cows after each of eight consecutive milkings. A cure was declared only if both post-treatment cultures, 3 and 5 weeks after therapy, were negative. Cure rates of 78–80% were obtained (VanDamme, 1983).

A case of bovine mycotic mastitis caused by *A. fumigatus* was successfully treated by combined intra-arterial and intramammary injection on three successive days of the antifungal drug miconazole. After evening milking 100 mg of miconazole (10 mL) was injected into the right external pudendal artery. Miconazole diluted with 50-mL saline was also infused into the affected udder (Katamoto & Shimada, 1990).

HORSE

In Equidae the most common fungal infections are caused by the dermatophytes *Trichophyton* spp. and *Microsporum* spp. They are infectious and can quickly spread from one animal to another. These dermatophytoses or ringworm are important diseases, more from the economic and prophylactic, than from the medical point of view. Generally they are self-limiting diseases and spontaneous healing occurs after 1–3 months. They are manifested in the form of superficial skin lesions and have normally no effect on the general state of the horse health (Van Cutsem & Rochette, 1991). Treatment of the affected horses remains necessary to shorten the duration and to reduce the severity of the infection. Moreover, the lesions reduce the aesthetic and sporting value of the horse and restrict its use. With a successful treatment of the horses and their environment, the spread of the disease to other horses, to other animals or even to humans is prevented.

Antifungal therapy of dermatophytosis includes mostly topical or oral treatment (Table 2). Horses have been treated with iodine shampoos, chlorhexidine shampoos, dilute bleach rinses, 5% lime sulphur solutions, undecylene acid and fungal orchard spray as a rinse. Older ready-to-use products with the active ingredient etisazol, or thiadiazine are no longer available for horses and were not always adequate. Neither etisazol nor thiabendazole suspension prevented fungi from being isolated from lesions (Pascoe, 1984).

There are also many topical salves and ointments on the market for other animal species or for human medication which contain miconazole, ketoconazole, clotrimazole or thiabendazole. The need to treat large numbers of horses dictate the use of solutions rather than ointments or salves because of ease of application and cost factors.

According to the European Consultation Conference on the availability of veterinary medicinal products only two substances – enilconazole and natamycin – will be left to treat ringworm and candidosis in horses. Following the loss of griseofulvin and ketoconazole in 1997, nystatin was also removed from the market on 1 January 2000. The European conference stated that over-restrictive regulation reduces medicines availability and increases off-label use.

Subcutaneous and systemic mycoses are rare in western Europe. Mostly they get the special attention of veterinary clinics, because these cases such as mycotic abortion, aspergillosis, candidosis, air sac mycoses and corneal stromal abscess, are complex conditions. In tropical and subtropical areas phycomycosis is quite common in horses and other animal species. Locally and sporadic maduromycosis, coccidioidomycosis; epizootic lymphangitis or rhinosporidiosis can be seen. The cure of these conditions requires mostly complicated and long-term treatment with amphotericin B or azoles and/or surgery.

Dermatophytoses (ringworm)

Dermatophytosis or ringworm is a superficial disorder caused by the fungi belonging to the genera *Trichophyton* and *Microsporum*. *Trichophyton equinum* is the most prevalent fungus. In horses, the girth is the most frequently affected region. The lesions vary. Usually they take the form of bare, squamous and flaking patches. In the initial stage of an infection the affected areas are hardly noticeable. The risk of transmission of *T. equinum* to people can be regarded as very low (De Vries & Jitta, 1973).

In racing stables, riding schools, stud farms, etc., measures should be taken to prevent all the horses from becoming infected. Wherever possible, infected animals should be quarantined. The infected animals should be given a full treatment, particular attention being paid to the lesions but preferably covering the entire surface of the skin. All equipment and utensils with which these animals have been in contact should be kept away from uninfected horses and disinfected with an antimycotic agent.

Table 2. Antifungal drugs in use * in horses

Antifungal (trade name)	Formulations	Indications	Treatment schedule
Amphotericin B	Injectable lotions 3%	*Aspergillus, Candida Histoplasma, Coccidioides Sporothrix, Mucor*	Daily long-term treatment (see specific indications)
Enilconazole Imaverol®	Emulsifiable solution	*Trichophyton, Microsporum*	Wash or spray with diluted emulsion (2000 p.p.m.) four times at 3–4-day intervals
Clinafarm®	Antimycotic disinfectant	(*Aspergillus*)	
Griseofulvin (Fulcin®; Fulvicin®; Griseo 100®)	7.5% Powder feed additive; bolus, liquid powder	*Trichophyton* (*Microsporum*)	Foal: 15 mg/kg/day 2–4 weeks; Pony: 10 mg/kg/day 1–2 weeks; or 10 g Griseo/100 kg bodyweight for 7 days, 3 weeks for *Microsporum*
Itraconazole (Sporanox®)‡	Pellets in capsules; i.v. *Candida, Aspergillus*	*Trichophyton, Microsporum*	See specific indications
Natamycin (Mycophyt®)	Suspension	*Trichophyton, Microsporum*	Topical 100 p.p.m. suspension; two times, with interval of pimaricin 4 days or spray suspension on the horse, repeat after 4–5 days; and 14 days later
Thiadiazine (Defungit®)†	Powder for dilution	*Trichophyton, Microsporum*	0.5% Dilution repeat two to three times with interval of 2–4 days; if no bensuldazin cure repeat schedule after 14 days
Thiabendazole (in 90% DMSO) Tresaderm®	4% Solution, ointment	*Trichophyton, Microsporum*	Washing with solution ointment for local lesions

*Drugs in bold are officially registered as veterinary products for horses; †registered for cattle; ‡human product.
DMSO, dimethyl sulphoxide.

Antifungal therapy of dermatophytosis includes only three registered products: natamycin, enilconazole and in some countries (e.g. Switzerland, USA) griseofulvin is still available for horses.

Natamycin

A suspension based on the antibiotic, natamycin, was applied by sponging to 83 horses of various breeds and ages with signs of clinical ringworm. Treatment successfully eliminated the disease within 4 weeks. After treatment the recovered animals did not show any evidence of re-infection for up to 6 months. The mycological clearance rate was 97%. It was also useful for treating the surroundings of the animals (Oldenkamp, 1979).

Enilconazole

Complete clinical cure was obtained with enilconazole emulsifiable solution in 96.4% of a total of 445 horses. All horses were treated four times with intervals of 3–4 days. Treatment usually consisted of washing the entire horse at the first application and only the affected areas and surroundings during the following applications. Clinical cure was complete between 1 and 10 weeks and new hair growth started between 2 and 5 weeks after the end of treatment. Incomplete results appeared to be related to incomplete treatment: the horse should be washed entirely at least once (De Keyser, 1981).

Thirty-nine horses with dermatomycoses were washed two times a week during 2 weeks with a 2% solution of enilconazole. The cure rate was: 48.7% after 2 weeks, 74.4% after 3 weeks; 92.3% after 4 weeks and 94.8% after 5 weeks. No side-effects were seen (Mayer, 1983).

Griseofulvin

Griseofulvin, the most commonly used systemic antifungal was licensed in many countries. Since 1997 it is no longer available in most European countries for horses because of recognition of griseofulvin toxicity and teratogenicity. Toxicity reactions appear to be idiosyncratic based on the findings of controlled studies (Kunkel & Meyer, 1987).

Long-term treatment with the antifungal antibiotic griseofulvin is moderately active against *T. equinum* and less well against *Microsporum* species. The effect of the therapy is uncertain and a combination with local treatment is mostly required (Frowijn & Kramer, 1987). The product is available for horses as a soluble powder or as a bolus. The powder is given like a drench or as a top dressing on feed at 10 g griseofulvin/100 kg body weight every day for 1 week. The micronized griseofulvin is given at 2.5 g to adult horses or 1.25 g to foals for not less than 10 days. It is not intended for use in horses for food.

Twenty-eight horses infected with *T. equinum* were administered 7.5 mg/kg griseofulvin mixed with mashed oats for 7 days (Reuss, 1978). The horses recovered 3–4 weeks after the end of

the therapy. *Trichophyton* ringworm disappeared in an additional 3–5 weeks in all animals. The product did not alter food intake.

Horses tolerate 100 mg/kg p.o. during 20 days without producing gross or microscopic lesions (Plumb, 1999). Possible side-effects after higher doses or long-term treatment include hepatopathy, anorexia, diarrhoea, cutaneous reactions and teratogenicity. In humans and animals griseofulvin is teratogenic.

Griseofulvin was given to pregnant horses during 30 days without side-effects. Nevertheless the manufacturer advises against treating pregnant animals especially during the first one-third of pregnancy (Allen *et al*., 1993; Heit & Riviere, 1995a).

Microphthalmia, brachygnathia superior, and palatocheiloschisis in a foal is reported after administration of griseofulvin to a mare during early pregnancy (Schutte & van den Ingh, 1997). Similar lesions have been described in other animal species after administration of griseofulvin during early pregnancy.

Keratomycosis

An evaluation of fungal specimens obtained from equine corneas over a 10-year period resulted in isolates from 13 different genera and 20 different species (Coad *et al*., 1985). The prevalent genus was *Aspergillus*. In another study *Aspergillus* organisms from nine of 10 such eyes were isolated (Gaarder *et al*., 1998). Fungal corneal stromal abscesses tended to be caused by yeast. Mycotic keratitis should be suspected when routine ulcer therapy is nonproductive. Specific antifungal treatment of horses with ulcerative keratomycosis should be based on history, results of ophthalmic examination, cytological findings, isolation of pathogenic fungi and known prevalence of unique ocular fungi in specific geographical area (Brooks *et al*., 1998).

Sweeney *et al*. (1984) cured stromal abscess in two horses. The successful outcome was largely a result of the frequent topical applications of antibiotics and the antifungals natamycin or miconazole in combination with the aggressive daily corneal epithelial scrapings.

The concentration of itraconazole in corneal tissue and aqueous humour after topical application of 1% itraconazole ointment and the effect of including DMSO in the ointment was studied in six horses. Corneal tissue concentrations averaged 1.1 μg/g in horses treated with the 1% ultramicronized itraconazole ointment and 7.9 μg/g for those treated with the 1% itraconazole/30% DMSO ointment. No itraconazole could be detected in the aqueous humour in either treatment group (Ball *et al*., 1997a).

Topical application of itraconazole-dimethyl sulphoxide ointment resolved keratomycosis in eight of 10 eyes, mean duration of treatment was 34.6 days. Thus itraconazole–DMSO ointment may provide an additional option for horses with keratomycosis (Ball *et al*., 1997b).

Upper respiratory mycotic infections

Upper respiratory mycotic infections like mycotic rhinitis and guttural pouch disease are caused by *Aspergillus*, *Conidiobolus*, *Pseudallescheria,* various species of other Zygomycetes. Nasal aspergillosis have been treated with natamycin, potassium iodine, amphotericin B and surgery.

Topical treatment with natamycin solution in three horses plus nystatin in two of the horses resulted in complete recovery in two cases but in one case the problem recurred (Greet, 1981). After treatment of 30 horses with guttural pouch mycosis by ligation of the internal carotid artery and lavage of the affected pouch with natamycin, 23 horses recovered fully (Greet, 1987).

Long-term treatment with itraconazole (3 mg/kg p.o. bid for 3–4.5 months) appears to be effective in the treatment of nasal aspergillosis because the fungal infection was eliminated in two horses with nasal granulomas. One horse with *Conidiobolus coronatus* nasal infections appeared resistant to itraconazole. No adverse reactions were noted in any of the horses during the treatment period (Korenek *et al*., 1994).

Chronic unilateral nasal discharge caused by *A. fumigatus* was treated with an indwelling through-the-nose-catheter with a rinse of enilconazole two times per day. This treatment resulted in complete recovery after 14 days (Van Nieuwstadt & Kalsbeek, 1994). Another successful treatment of guttural pouch mycosis with itraconazole and topical enilconazole in a horse is reported by Davis and Legendre (1994).

A horse with a mycotic plaque in the nasal cavity caued by *Pseudallescheria boydii* was treated with 2% miconazole intranasally, sodium iodide i.v. and potassium iodide p.o. Thirty and 60 days after treatment was initiated, the nasal cavity was found to be free of infection (Davis *et al*., 2000).

Coccidioidomycosis

This is a fungal disease that occurs in arid and semiarid regions of North and South America. Treatment of equine coccidioidomycosis has been unsuccessful. In a retrospective study of 15 confirmed cases, Ziemer *et al*. (1992) stated that even prolonged treatment with specific antifungals such as amphotericin B was without benefit. Long-term therapy of amphotericin B is limited because of its nephrotoxicity (Drouhet & Dupont, 1987).

Ketoconazole is not absorbed well from the digestive tract of horses and has not been effective in the treatment of *Coccidioides immitis* in horses (Prades, 1989).

Foley and Legendre (1992) treated a horse with coccidioidomycosis osteomyelitis with itraconazole orally (2.6 mg/kg) every 12 h for 90 days. The horse was almost normal after 90 days. Five months after discontinuing itraconazole treatment severe neck pain and neurological signs recurred. The horse was treated for an additional 6 months and her condition improved to almost normal for 2 years. There was no evidence of drug toxicity.

Sporotrichosis

Equine sporotrichosis has been successfully treated with griseofulvin. In a first treatment of approximately 20–25 mg/kg griseofulvin was administered orally for 2 weeks. Then the dose was reduced to approximately 10 mg/kg for an additional

46 days (Davis & Worthington, 1964). An antifungal therapy in an Arabian horse with sporotrichosis stopped the extension of the granulomata (Greydanus-van der Putten *et al.*, 1994).

Phycomycosis (Pythiosis, basidiobolomycosis, conidiobolomycosis)

This old collective name 'phycomycosis' covers various fungal infections caused by *Hyphomyces destruens* and mucorales such as *Rhizopus* and *Conidiobolus* species. Pythiosis occurs in South America, Australia and the USA.

The most common treatment of equine pythiosis has been the surgical removal of the lesions. This method is very popular and frequently used by veterinary practitioners. Because of the incomplete removal of the *P. insidiosum* hyphae from the affected tissues, a common short-coming of surgical treatment is its high rate of recurrence. More importantly, lesions of the limbs are very difficult to treat by surgery.

Amphotericin B was the first available drug for systemic fungal infections, such as phycomycosis. It was used systemically or locally, or both, in the treatment of localized subcutaneous phycomycosis in horses (McMullan *et al.*, 1977).

A case of conidiobolomycosis with severe granulomatous lesions of the upper airways that were attributable to *Conidiobolus coronatus* was successfully treated with intralesional and topical use of amphotericin B and with surgical extirpation. It was documented by clinical examination of the horse, 4 years after treatment (French *et al.*, 1985).

Nasopharyngeal conidiobolomycosis may be treated successfully with intralesional injection of amphotericin B in combination with administration of sodium iodide and potassium iodide, but there is a possibility of recrudescence of infection (Zamos *et al.*, 1996).

A nonhealing wound with bone lesions in a pregnant mare revealed *Pythium* sp. The mare was treated by regional arterial fusion with miconazole and excision of affected soft tissues and the distal two-thirds of metacarpal bone i.v. The mare recovered without complications and gave birth to a healthy foal (Worster *et al.*, 2000).

Epizoötic lymphangitis (Histoplasma farciminosum)

In his review of epizootic lymphangitis al-Ani (1999) mentioned amphotericin as the drug of choice for the treatment of clinical cases. A 5-week regimen of amphotericin B administered intravenously resulted in clinical recovery (Cornick, 1990).

Maduromycosis (Mucor, Absidia)

Reid *et al.* (1977) published a successful treatment of a maduromycotic fungal infection of the equine uterus with amphotericin B.

Candidosis (Candida spp.)

Equine endometrial candidosis was successfully treated with amphotericin B (Brook, 1982).

Systemic candidosis diagnosed after *Candida albicans* was isolated from specimens obtained from one or more internal sites in four foals. The three foals in which treatment was attempted responded well to i.v. administration of amphotericin B and/or oral administration of fluconazole (Reilly & Palmer, 1994).

Joint infections caused by *Candida* spp. in two horses was resolved after i.v. administration of amphotericin B and joint drainage (Madison *et al.*, 1995).

Other new antimycotics such as fluconazole may be appropriate agents for treatment of fungal infections in horses. Bioavailability of fluconazole was high after oral administration to horses. Long-term oral administration maintained plasma and body fluid concentrations above the mean inhibitory concentrations (8.0 mg/mL) reported for fungal pathogens in horses (Latimer *et al.*, 2001).

PIGS

Only a few dermatophytes attack pigs, and even these strike only sporadically. Swine ringworm is caused by the dermatophytes *M. nanum, M. canis,* possibly *M. gypseum*, and by *T. mentagrophytes*. In pigs ringworm is rare in Western Europe, but there are entire herds infected by *M. nanum* in the USA and New Zealand.

Microsporum nanum infections are more common in outdoor sows and boars. The pigs are infected from the soil by this geophilic dermatophyte. It can often be isolated from the soil in pig yards or runs. Accidental infections with *M. canis* and *T. mentagrophytes* are caused by infected rats, dogs, cats, and even humans, carrying the infection into the pigsty.

Swine ringworm lesions are usually circular and enlarge centrifugally. They differ from some types in that no alopecia exists and the infections do not tend to disappear spontaneously (Ginther *et al.*, 1964). Ringworm lesions in pigs are easily hidden by dirt or a full growth of hair and are easily confused with urine stains. They begin as small reddish brown foci, 1–2 cm in diameter, that spread concentrically and may reach up to 12 cm in diameter. Foci may be covered with a thin loose crust and may be either single or coalescent. They may occur anywhere on the body but are most commonly found behind the ears.

The economic importance of swine ringworm to the pig industry cannot be determined at this time. Human infections with *M. nanum* are rare in the literature (de Camargo *et al.*, 1992). Ringworm, which is more common in outdoor pigs, poses a little risk to humans and generally would cause only mild, readily treated lesions. Hog farmers infected by *M. nanum* were successfully treated with clotrimazole or miconazole cream, sometimes combined with griseofulvin (Roller & Westblom, 1986; Alexander, 1998).

Treatment is mostly not necessary, but when treatment is performed it involves topical solutions or oral griseofulvin. First, the thick crusts should be removed gently with a brush and mild soap, and the contaminated material burned. Topical therapy includes washes or sprays of 0.5% lime-sulphur, 0.5% sodium

hypochlorite (1:10 chlorine bleach), 0.5% chlorhexidine solution, 1% povidone-iodine, or 1:300 captan. These medications are applied to the entire body surface of affected animals daily for 5 days, then weekly until the infection is controlled (Hollis, R. J. personal communication).

No antimycotics are registered for swine in the European Community. In Switzerland griseofulvin is recommended at 20 mg/kg daily during 6 weeks (Plumb, 1999); or 1 g/100 kg during 30–40 days (Heit & Riviere, 1995a). Off label use of griseofulvin has been used as an ointment.

A spray with enilconazole (0.2% emulsion) followed by a second and third treatment at 4-day interval was assessed in two trials in an attempt to cure the lesions caused by *T. mentagrophytes*. Results were in all cases negative, probably because of the sebum deposit which builds up on the skin and prevents adequate penetration of the product (Wilkinson, 1985).

After treatment the pens should be thoroughly disinfected with an antimycotic disinfectant before fresh stock is introduced.

Candidosis

Yeast infections caused by *Candida* species, and especially by *C. slooffii* and *C. albicans*, occur quite often in pigs after prolonged therapy with antibacterial antibiotics or when they are fed an incorrect diet. In a large Bulgarian study, 2.5% of a total of 1200 piglets, showing no clinical signs of skin or hair diseases, were *Candida* carriers (Stankushev & Duparinova, 1976).

Typical clinical signs are a white to yellow adhering film in the mouth and on the tongue, together with a greatly increased gastrointestinal yeast flora. These infections are not infrequently fatal to suckling pigs.

No registered therapy is available for candidosis in pigs.

POULTRY AND BIRDS

In poultry and birds, dermatophytes are less important pathogenic fungi than in most other domestic animals. The only dermatophyte of any consequence, *M. gallinae* (*T. gallinae*), only occurs sporadically causing fowl favus or comb disease in chickens, turkeys and ornamental birds. It is generally confined to the unfeathered parts of the head and is manifested by a greyish white, granular layer on the comb and wattles. It tends to strike free-range chickens and other poultry living loose in yards or runs, more often than those kept under battery conditions of industrial poultry farms (Bradley *et al.*, 1993).

Aspergillosis or brooder pneumonia is predominantly an infection of the respiratory system. The causative organism is mostly *A. fumigatus* and in some cases *A. flavus*. These are ubiquitous opportunistic saprophytes which can turn pathogenic, not only in birds but also in large domestic animals, and in humans. In young birds, aspergillosis may occur in acute attacks; there is a high mortality rate in the early days of life and lasting morbidity. In adult poultry, the affection occurs in a chronic form characterized by granulomatous infection lesions in the lungs and air sacs. Cracked and dirty eggs are known to become affected in industrial hatcheries. Death in shell embryos occur and the newly hatched chicks are severely affected, as evidenced by mortality, slower growth and morbidity (O'Meara & Chute, 1959). Ornamental birds and wild birds in captivity, such as canaries, parrots and penguins are highly susceptible and easily die of aspergillosis.

Indirectly, the toxic metabolites of aspergilli contaminate feed stuffs. These mycotoxins are the causative agent of turkey 'X' disease, so called because it affected thousands of turkey poults in the UK in 1960 when its aetiology was unknown (Robb, 1993).

Yeasts belonging to the genus *Candida* are generally harmless opportunistic saprophytes, but they can cause both superficial and mucocutaneous fungal infections in chickens, turkeys, domesticated Guinea-fowl, partridges, pheasants, black grouse, pigeons and parrots. A mycological survey of the crops of approximately 100 healthy broiler chickens revealed that the incidence of *Candida* in the crops ranged from 17 to 52%. Less than 1% exhibited visible lesions attributable to *Candida*. *Candida albicans* comprised 95% of the isolates (Wyatt & Hamilton, 1975).

Fowl candidosis (thrush, crop mycosis) is mostly caused by *C. albicans* (Stankushev *et al.*, 1978). It primarily affects the upper digestive tract of all birds and is characterized by whitish thickened areas of the crop and proventiculus, erosions in the gizzard, and inflammation of the vent area. *Candida albicans* can cause eye disease in ducks and crop mycosis in different water fowl species. It is a common problem in nestlings, particularly hand-fed psittacins.

A very common dermatitis among poultry workers: 'chicken poison disease' is caused among other things by *C. albicans* infections (Marks *et al.*, 1983).

Cryptococcus, a pathogenic yeast to humans, is often found in old excrements of pigeons, parakeets and numerous aviary birds, but is only slightly pathogenic to birds.

In their review of antifungal agents in avian species, Orosz and Frazier's (1995) special formulations and dosage regimes of the modern antimycotics are given for ornamental birds, psittacines, parrots, parakeets and raptors. They stated that treatment of fungal infections in birds remains a challenge. Veterinarians need to reconsider their approach to therapy for mycotic infections because of the difficulty in diagnosis, the usually advanced stage of fungal infection when the bird is first presented, and the limited knowledge regarding pharmacokinetics and appropriate dosage regimes for birds. A selection of different therapeutic possibilities for aspergillosis, candidosis and dermatophytosis in birds is also given by van den Bergh and Van Cutsem (1993). An overview of antifungal drugs of use in poultry and other birds is presented in Table 3.

Fowl favus

There are no labelled-for-poultry products for the treatment of favus. Bradley *et al.* (1995) reported complete cure in a flock of various Oriental breed and crossbreed chickens after treatment with an ointment of miconazole nitrate 2%. The birds received the treatment twice a day for 34 days and were all negative for *M. gallinae*.

Table 3. Antifungal drugs in use in poultry and birds

Antifungal (trade name)	Administration route	Indications	Treatment schedule
Amphotericin B*	Injectable lotions 3%; i.v., intratracheal, nebulization	*Aspergillus*, *Candida*	1.5 mg/kg q 12 h, 5–7 days; 1 mg/kg q12 h, 5–7 days 1 mg/mL, 15 min†
Clotrimazole*	Nebulization solution	Aspergillus	45 min/day in raptors†
Fluconazole*	Oral (tablet, aqueous solution)	Systemic *Candida*	Empirical 2–5 mg/kg, q 24 h, 7–10 days†
Flucytosine*	Oral	*Aspergillus*	Oral: 75–120 mg/kg, q6 h, 50 mg/kg q 12 h, 2–4 weeks†
Enilconazole (Clinafarm®)	Spray	*Aspergillus* in hatcheries	Spray: 20 mg/m^2 of wall area, i.e. 10 L of the ready-to-use smoke generator solution (1/100 or 0.15% dilution) per 750 m^2 or per 3000 m^3 Smoke: one smoke generator is sufficient for 50 m^3
Itraconazole*	Oral solution, pellets in capsules	*Aspergillus*, *Candida*	10 mg/kg every 24 h, 14 days minimum
Ketoconazole*	Oral (tablet)	*Candida* (*Aspergillus*)	30 mg/kg q 12 h, 14–30 days†
Miconazole*	Nebulization solution	*Aspergillus*	45 min/day in raptors†
Nystatin*	Oral in feed, tablet, suspension, injection	*Candida* GI tract, skin	100 000–300 000 IU/kg q 12 h, 7–10 days with antibiotic therapy
Parconazole (Parcomyc®)	Powder in feed	*Candida* (trush) guinea fowl	Prophylactic: 30 mg/kg feed; therapeutic: 60 mg/kg feed for 7–10 days
Thiabendazole (Fungitec®)	Smoke tablet	*Aspergillus*	

Drugs in bold are registered for veterinary use; *human products, †dosage regime according to Orosz and Frazier (1995).

Aspergillosis

In the battle against aspergillosis, the role of specific antimycotic disinfectants in the prevention of airborne infections by fungal pathogens is crucial. Complete elimination of infectious germs can only be approximated in the sterile operating theatres of a hospital (Hay, 1991). Sterility cannot be achieved in hatcheries with hundreds of thousands of chicks hatching, surrounded by down feathers and dust in ideal temperature and humidity. Unremitting discipline and a strict disinfecting programme with treatment of incubators, hatching machines and hatching compartments using smoke generators and sprayers is required (Rochette, 1985; Desplenter, 1988).

There is no treatment for clinical aspergillosis in poultry and birds in affected flocks. Cleaning and disinfecting the equipment is often helpful.

Individual birds can sometimes be treated successfully with surgical removal of the aspergillomes and/or long-term dosage regimes of azoles or amphotericin B and flucytosine (Orosz & Frazier, 1995).

Thiabendazole

In some countries, thiabendazole is available as a smoke pellet or smoke generator formulation for application in chicken hatcheries and poultry houses (Desplenter, 1988). Drinking water medicated with thiabendazole is ineffective against *A. fumigatus* (Klimes & Kriz, 1968).

The *in vitro* activity of thiabendazole, 5-fluorocytosine and amphotericin B was tested against 11 isolates of *A. fumigatus* from avian species. Additionally, the plasma concentrations of these drugs were determined in turkeys, hawks and owls. Thiabendazole inhibited most isolates *in vitro* at concentrations between 25 and 50 μg/mL. The mean minimum inhibitory concentration for 5-fluorocytosine was 2.73 μg/mL and for amphotericin was 0.81 μg/mL, respectively. Thiabendazole MICs were not reached in the plasma of any species. For amphotericin B and 5-fluorocytosine MICs were found 2 and 6 h postadministration, but not at 24 h (Redig & Duke, 1985).

Groups of chicks, 1–3 days old, experimentally infected with *A. fumigatus*, received thiabendazole either in feed or drinking water for 17 days, or once daily as an aerosol for 4 or 14 days. Mortality was significantly reduced in groups treated with aerosols containing 0.02 and 0.04 g thiabendazole per litre of air, or with food containing 0.037–0.225% thiabendazole, provided treatment was initiated immediately after infection (Klimes & Kriz, 1968).

Fumigation with thiabendazole tablets containing 7 g thiabendazole eliminated temporarily the moulds *A. fumigatus* and *A. flavus* from the incubators and hatcheries from chicken and turkey farms in Egypt. But after fumigation the number of dead-in-shell embryos remained high (25.6%) and the rate of hatchability was only slightly higher in the fumigated group in comparison with the nonfumigated group (Saif & Refai, 1977).

Amphotericin B

Treatment of clinical aspergillosis with amphotericin B alone or in combination with flucytosine has been disappointing in general. It has been used to treat fungal infections systemically and topically in birds. The intravenous formulation has been given i.v., injected into the trachea using a catheter, or injected directly into an affected air sac. The intravenous formulation has also been used as a nebulization solution for raptors and psittacines (Orosz & Frazier, 1995). As amphotericin B is rapidly

excreted, it is given over at least several days to obtain active plasma concentrations (Redig & Duke, 1985).

Compared with mammals the toxicity of amphotericin B in birds is low. A fatal treatment of sinusitis with severe granulomatous reaction in the infraorbital sinus of an African grey parrot was noted after it was used in a solution that was flushed through the nares (Vandermast *et al*., 1990).

Flucystosine

It has been administered most commonly in combination with amphotericin B because of synergistic effects. It has been used therapeutically and prophylactically in raptors, swans, cockatoos and turkeys. It is given orally during 3–4 days to obtain active plasma concentrations. Toxicity is low. In some birds complaints of digestive disturbance are noted (Redig & Duke, 1985). About 50% of the *Aspergillus* strains and *C. albicans* strains are resistant to flucytosine (Dorrestein *et al*., 1985; Orosz & Frazier, 1995).

Nystatine

Nystatine given in feed, or by injection, had good results in water fowl in captivity (O'Meara & Witter, 1971).

Aspergillosis in turkeys is very often associated with contaminated litter. Severe mortality occurred in a flock of 16 000 turkey poults after fresh litter was added to the brooder house. After treating the added litter with nystatin and copper sulphate the mould count dropped and mortality was also reduced, but not to preinfection concentrations. Despite treatment, performance of the flock remained poor (Dyar *et al*., 1984).

Enilconazole

Enilconazole possesses potent aspergillicidal activity not only by direct contact, but also in its vapour phase (Van Gestel *et al*., 1981; Van Gestel & van de Ven, 1984; Van Gestel, 1986). It can be used for topical treatment but also for disinfecting the environment, or for the prevention of airborne infections (Desplenter & Marsboom, 1980; Van Cutsem *et al*., 1988, 1989).

The fungicidal activity of thiabendazole and enilconazole was evaluated and compared in experiments with conidia of *A. fumigatus* in hanging and lying drops with 5×10^6 spores per drop. Enilconazole at concentrations of 0.146 and 0.254 g/m^3 was highly fungicidal to the spores, while thiabendazole at 0.409 and 0.475 g/m^3 was not fungicidal. Thiabendazole reduced only the number of viable spores in lying drops and was poorly active in hanging drops (Van Cutsem *et al*., 1988).

In a controlled *Aspergillus* challenge model simulating field conditions of mould growth in embryonic eggs the potential of different fungicides was evaluated. Fungicides and mould inhibitors used for injection included two feed additives which contained propionic acid, a phenol, a quaternary ammonium compound, hydrogen peroxide, enilconazole and an aromatase inhibitor (azole derivative). Only enilconazole and the aromatase inhibitor significantly reduced the concentration of air cell membrane infection with *A. fumigatus*. All other products tested significantly increased the concentration of air cell contamination (Williams & Brake, 1996).

Fumigation with enilconazole smoke was highly successful in preventing mortality, in reducing morbidity, and in neutralizing growth inhibition of day-old chickens infected with various inoculum sizes of airborne spores of *A. fumigatus* (Van Cutsem, 1983; Van Cutsem *et al*., 1989).

In a hatchery with severe problems of aspergillosis four vaporizations with enilconazole eliminated the infections for nearly 2 months. Two further vaporizations reduced the infection to a very low concentration for about 3.5 months (Desplenter, 1988).

The efficacy of enilconazole for disinfecting hatcheries contaminated with *A. fumigatus* was evaluated in young chicks and Japanese quails with clinical aspergillosis. In the quail farm mortality during the first days of life was 30%, and 94% of the birds had lesions. A continuous disinfection programme of the hatchery rooms, incubators and hatching machines with enilconazole spray and smoke generators led to the elimination of the disease. After 10 weeks the mortality in the quail farm was reduced to 4% and only 10% had still lesions. In the chicken farm a nebulization with 50 mg enilconazole/m^3 reduced the infection pressure drastically, as measured by the number of colony forming units on the plates (Braem, 1986).

Aspergillosis in chickens and turkeys is mostly associated with contaminated litter. Cleaning and disinfecting of the environment with an antimycotic agent can control the infection. In a flock of chicks the number of birds dying per day from infection with especially *A. flavus* increased to 1% during the second half of the fattening period. After cleaning and disinfecting with enilconazole the concentrations of *A. flavus* were reduced to zero (de Wit *et al*., 1993).

A control programme with enilconazole smoke and spray in the tropical areas of the Dominican Republic reduced the high mortality rates (up to 56%) of lung aspergillosis in young chickens (Barboza *et al*., 1993).

Enilconazole was used in the course of a spontaneous outbreak of aspergillosis in a broiler flock. Up to the tenth day of life the total mortality was 8% and the surviving broilers had a lower body weight. A single treatment via spray in a dose of 1.5 g enilconazole/10 m^2 housing floor space reduced mortality from the second day after treatment and the body weight returned to normal. According to the authors, the success of the treatment depends on an early diagnosis and immediate start of therapy (Redmann & Schildger, 1989).

Ketoconazole at 50 mg/kg during at least 3 weeks gave good results in ducks (Tiel, 1990).

Clotrimazole in combination with itraconazole has been used for the treatment of aspergillosis in raptors. Clotrimazole was suspended in polyethyleneglycol (PEG) 300 and nebulized for 45 min daily (Pappagianis & Reavill, 1994).

Itraconazole

Compared with other azoles, itraconazole has improved activity against *Aspergillus* spp. (Van Cutsem *et al*., 1984). It is, with or

without amphotericin B, the first choice for treatment of aspergillosis in birds. It has been used in a variety of raptors, psittacines and waterfowl at 10 mg/kg every 24 h for 10 days. No toxicity has been reported in birds. The half-life time in parrots was 6 h, whereas the half-life in pigeons was approximately 8 h (Orosz & Frazier, 1995; Martin, 1999).

Fluconazole

Fluconazole has not been thoroughly evaluated for treatment of aspergillosis. It has been administered at 2–5 mg/kg q 24 h to psittacine species with candidosis with excellent results (Flammer, 1994).

Various treatments for aspergillosis in ostriches have been attempted, including amphotericin B, flucytosine, nystatin, miconazole and itraconazole. There are no reports of successful treatment in ostriches (Marks *et al*., 1994). Surgical removal of the aspergillomes combined with a long-term treatment with itraconazole (10 mg/kg) or flucytosine and amphotericin B is necessary. Disinfection of the cages with enilconazole smoke and spray is advised as prevention (Arts *et al*., 1995).

Candidosis (thrush)

Nystatin. Nystatin has been used for the treatment of candidosis of the crop and/or gastrointestinal tract in birds. Empirical doses of 100 000–300 000 IU/kg q 8–12 h for 7–10 days have resulted in the successful resolution of candidosis. Regurgitation following nystatin administration may be the result of taste, not toxicosis. Adult birds require large volumes (1–2 mL), therefore gavage may be necessary (Orosz & Frazier, 1995).

Nystatin has been dispensed in the drinking water of turkeys with sodium lauryl sulphate. A concentration of 62.5–250 p.p.m. was found to be beneficial in treatment of crop mycosis (Huber, 1991).

Parconazole

Parconazole is used for the treatment of candidosis in guinea fowl. It is used prophylactic as medicated feed at a concentration of 30 mg/kg feed or therapeutically at 60 mg/kg feed, around the ages of 3–4 weeks for 7–10 days.

Parconazole is of low toxicity, the maximum daily intake of residues for the consumer is below the ADI (acceptable daily intake), even 24 h after treatment (Levron *et al*., 1985).

Ketoconazole

Ketoconazole has been used for systemic and for localized yeast infections. Administered orally and topically in various experimental models it was efficacious against *C. albicans*. Scanning and transmission electron micrographs of infected tissue demonstrated the speed with which *C. albicans* was eradicated from the host (Thienpont *et al*., 1980). Oral treatment with ketoconazole prevented and cured crop candidosis of turkeys. It was also highly effective against systemic candidosis in chickens (Thienpont *et al*., 1979). No toxic reactions were observed in pigeons administered ketoconazole at 30 mg/kg q 12 over a 30-day trial or in Amazon parrots, given the same dose for 14 days (Kollias *et al*., 1986).

RODENTS, RABBITS AND FUR ANIMALS

Rodents, lagomorphs and fur animals are widely used as laboratory animals, source of meat and fur, and increasingly, as pets. Skin diseases are the most common cause for the visit to the veterinarian. Most of these skin conditions are because of a wide variety of fungi, bacteria and viruses. The importance of mycotic diseases in these animals depends on their environment and life style. The carriage of ringworm by laboratory animals and industrialized fur bearing animals is well-documented. Outbreaks of ringworm in breeding colonies, industrialized rabbits and fur animals in farms can cause serious economic damage.

In wild animals, skin diseases cuased by ringworm infections are less common when they are living in their natural environment. The isolated fungi from wild animals from the families of *Muridae* and *Microtinae* are mainly moulds such as *Aspergillus* and saprophytes, but *Candida* spp. and dermatophytes could be found. While none of the animals investigated showed signs of apparent mycosis some of the fungi might be infectious for other animals and even humans (Barnaszkiewicz, 1985).

In rodents and fur animals living as a pet in households, skin diseases cused by ringworm infections are quite common in rabbits, guinea-pigs, chinchillas, hamsters, rats and mice (Böhm & Bisping, 1968; Weisz & Weber, 1983).

Although the antifungal activity of modern antimycotics are investigated in experimental fungal infections of laboratory animals, only a few products are developed as an antifungal in practice for those animals. The limited data of interest for the practitioners of these antimycotics for these ‘orphan animals’ are summarized per animal species (Table 4).

An alternative for some animals is vaccination. Immunization of fur-bearing animals (silver fox, foxes, polar foxes) and rabbits with a Russian vaccine can prevent trichophytosis (Sarkisov & Nikiforov, 1981).

Ferrets

Ringworm cuased by *M. canis* can infect young ferrets and may be transmitted to them from cats (Hagen & Gorham, 1972). Skin lesions with alopecia, scaling and crusts can cover the whole body. In young ferrets ringworm caused by *M. canis* can be lethal (Moorman-Roest & Lumeij, 1987). Clinical signs tend to be transient; however, the organisms will persist in a subclinical state. Spontaneous cure is possible.

Oral treatment with 25 mg/kg griseofulvin during 3–4 weeks can be applied (Kraft, 1984), or with griseofulvin at 25–50 mg/kg daily during 4 weeks (Ryland *et al*., 1983; Gabrisch, 1995; Wenzel, 1996). Antifungal shampoos and topical lotions can be given.

Table 4. Antifungal drugs in use * in rodents, rabbits and fur animals

Animal species	Indications	Treatment schedules
Chinchilla	*T. mentagrophytes, M. canis*	Miconazole, clotrimazole, tolnaftate powder in sandbox Griseofulvin 25–50 mg/kg during at least 3 weeks
Ferret	*M. canis*	Antifungal shampoo or topical solution Griseofulvin 25–50 mg/kg during 3–4 weeks
Guinea-pig	*T. mentagrophytes, M. canis*	Rubbing miconazole powder in the fur; ketoconazole cream Itraconazole: oral solution 5 mg/kg by gavage Ketoconazole 10 mg/kg p.o. twice a day Griseofulvin 25–50 mg/kg during 3–5 weeks
Hamster	*T. mentagrophytes, M. canis*	Miconazole powder in sand Washing with enilconazole solution twice a week for 3 weeks Itraconazole, oral solution 5 mg/kg by gavage Griseofulvin 30 mg/kg during 1 month
Rabbit	*T. mentagrophytes, M. canis*	Rabbit farms: 50 mg/m^2 enilconazole spray on surface and animals, twice a week – preventive:1 enilconazole smoke generator/50 m^3 Individually: griseofulvine:25–30 mg/kg during 5–6 weeks: or 350 p.p.m. in feed
Rat and mouse	*T. mentagrophytes, M. canis*	Local antimycotic ointment Oral griseofulvin 25–30 mg/kg during 30 days

*Not licensed for these animals; off label use.

Guinea-pigs

Among all laboratory animals, the guinea-pig is the most susceptible to ringworm caused by *T. mentagrophytes*. Ringworm infections in guinea-pigs are recorded all over the world and outbreaks of ringworm in breeding colonies are quite common. In household pet animals inapparent infection is common with hair loss, crusts on back, face and ears. Lesions in guinea-pigs tend to heal in 2–6 weeks. Both healthy and animals with lesions may serve as reservoirs of *T. mentagrophytes* and transmit the infection to humans (Fischman & Portugal, 1971).

In the seventies even the use of the most 'effective' treatment was destroyed all infected animals (Rush-Munro *et al.*, 1977). Nowadays infected animals can be treated with topical ketoconazole cream daily for 2–4 weeks and griseofulvin 20 mg/kg for 25 days (Noonan, 1994).

Griseofulvin can be given alone at 25 mg/kg during 2–4 weeks (Kroker, 1999), or to support the local therapy with doses of 30–50 mg/kg griseofulvin during 4–5 weeks (Wasel, 1995). Some authors are recommending high doses of griseofulvin: 75 mg/kg for 3–4 weeks (Wasel, 1995) or even 100 mg/kg (Harvey & Clark, 1995).

Butenafine for 10 days, or miconazole for 2–4 weeks can be applied as topical treatment.

In a comparative study, oral itraconazole vs. topical bifonazole in experimental dermatophytosis was assessed in guinea-pigs. Fungi located in the hair sheaths were affected only by the oral treatment with itraconazole, which not only prevented invasion of the inner hair structures and inflammatory responses but also led to a complete clearance of the infection within 7 days (Borgers *et al.*, 1993).

To give the necessary care correct the poor husbandry, overcrowding and stress.

Hamsters

High incidence of skin infections with *T. mentagrophytes* can be found in laboratory colonies of hamsters (Young, 1974).

Disinfecting the cages and new bedding material is necessary. After hair clipping around the local lesions, washing the hamster with enilconazole (Imaverol®) is very effective (Tack & Zwart, 1988). Oral griseofulvin 30 mg/kg daily during a month results in effective control (Allen *et al.*, 1993). Griseofulvin can also be given in drinking water at 25 mg/kg during 14 days (Wasel, 1995).

Mice

It is known that clinically healthy mice can be carriers of dermatophytes. Various fungi have been isolated from the skin of free living mice, for example *Aspergillus*, *Trichophyton*, *Penicillium*, *Rhizopus* and Mucorales. Laboratory and wild mice are usually infected by *T. mentagrophytes*, the main causative agent of ringworm in this species. The classical ringworm of the mouse or 'mouse favus' is caused by *T. quinckeanum* and *T. mentagrophytes* (Cuturic, 1969; Cuturic & Hajsig, 1969).

Ringworm is mostly subclinical. Patchy hair loss, white crusted lesions and erythema can be seen in the neck, back and base of the tail. This should not be confused with barbering which happens when mice gnaw each other's fur and cause bald, often symmetrical patches.

Mice subjected to dipping or washing with antimycotic solutions must not be returned to mesh cages as they die, apparently of cold. They can recover from immersion in solid-sided boxes. An antimycotic ointment can be applied on local lesions.

To cure the affected animals, 30 mg/kg griseofulvin is given daily during 1 month mixed in the feed (Visser, 1995).

Rats

Ringworm is less common in pet rats, kept individually. However, *T. mentagrophytes* can be detected in large groups of laboratory rats. The usual wholesale slaughter program after an outbreak in rat breeding stock can be avoided with a strict control programme and treatment (Mizoguchi *et al*., 1986). *Trichophyton mentagrophytes* and *M. gypseum* have been recorded. Typical cutaneous lesions on the back are alopecia and hyperkeratosis.

An antimycotic ointment can be applied on local lesions combined with daily oral dose of griseofulvin 25 mg/kg during 4–6 weeks (Wijnbergen, 1986; Allen *et al*., 1993).

Fur animals

In fur animals bred in captivity such as silver fox, arctic fox, chinchilla, mink and weasel, ringworm depreciates the commercial qualities of the furs and upsets the breeding of pedigree animals. The main causative organisms are *T. mentagrophytes* and *M. canis* (Zimmermann & Haufe, 1971; Hagen & Gorham, 1972). Fungal infections are often present in a latent form in fur-breeding units (Böhm & Löliger, 1969). Sudden outbreaks of *T. mentagrophytes* ringworm can cause serious damage in silver fox or mink farms.

In chinchillas, *T. mentagrophytes* has been reported as a cause of 'fur slipping'. Although *M. canis* and *M. gypseum* have been incriminated in outbreaks of ringworm, *T. mentagrophytes* has been recovered from most cases (Male & Fritsch, 1966). Mild cases will often heal spontaneously, but more advanced infections are best treated with oral or topical antimycotics.

Griseofulvin therapy at a daily dose of 25–40 mg/kg bodyweight at least during 3 weeks was effective in treating and preventing ringworm caused by *T. mentagrophytes*, *M. canis* and *M. gypseum* in chinchillas and rabbits (Hagen & Gorham, 1972; Schweigart, 1995).

Providing each animal its own sandbox is the best prevention. The sand can be sterilized by heating it in the oven at 200 °C (van der Hage & Bakker, 1994). About one tablespoon of medicated powder for athletes foot (miconazole, clotrimazole, tolnaftate) can be added to the dust bath, but should be used with caution.

Rabbits

After rabbit farming was industrialized the incidence of dermatomycosis drastically increased. In most cases, *M. canis* and *T. mentagrophytes* are isolated. The infections spread rapidly resulting in poor conditions of the young rabbits with considerable morbidity and economic losses (Rosell *et al*., 1985; Van Cutsem *et al*., 1985).

Clinical manifestations of ringworm are normally first detected in young rabbits 3–6 weeks old. The lesions may appear anywhere on the body, although most are generally located on the muzzle, around the eyes and the ears, the front legs and on the back. The whole circular raised reddish patches are covered with white bran-like or flaky scales. Typical clinical signs also include loss of hair, thinning of hair and bald patches, with crusts and broken-off hairs (Van Cutsem & Rochette, 1991).

The infected animals present a permanent source of zoonotic infections of the attendants and their family members.

In the light of the work of the Russian investigators Sarkisov and Nikiforov (1981), the prevention of ringworm in rabbits by means of vaccination appears possible but the results are as yet uncertain.

As the rabbit is highly sensitive to stress treatment, dipping and individual spraying has to be avoided. Disinfecting of the environment is an alternative. Environmental disinfection of the animal houses, equipment, cages, etc. with a spray or a smoke generator containing an antimycotic can reduce the infectivity of the environment and eventually even eliminate the infection.

In two rabbit farms in which clinical ringworm had been confirmed, the walls and ceiling were disinfected with enilconazole spray 15%. Ringworm was found to be present in 23.4% of the 826 rabbits in the first farm and another 35.7% in the second. After spraying, twice a week for 4–6 months with 50 mg enilconazole per squaremetre the infection decreased rapidly, falling below 1%. Even after treatment, the infection pressure was very low, witness the small number of both colonies per Petri dish and positive animals (Van Cutsem *et al*., 1985).

In six clinical trials in rabbit farms from Belgium, the Netherlands, Italy and Spain, a dose of 50 mg/m^2 enilconazole was applied. The treatment was carried out twice weekly in batteries filled with rabbits and was continued for at least 3 weeks. The control of the ringworm infections in those rabbit farms was possible by disinfecting the environment alone, without topical or systemic treatment of the rabbits themselves (Rochette & Van Meirhaeghe, 1997). Enilconazole acts both fungistatically and fungicidally, furthermore, it is active in its vapour phase (Van Gestel *et al*., 1981). This may largely contribute to the results obtained in eliminating ringworm in the rabbits without having to resort to direct treatment. The results were stable to the extent that the earliest relapse occurred 3–4 months after the end of the treatment (Rochette & Van Meirhaeghe, 1997).

In individually kept rabbits oral dose of griseofulvin 25–30 mg/kg bodyweight once daily during 5–6 weeks is given (Schall, 1995; Smith & Burgmann, 1997). In case of local lesions, topical treatment is preferred with miconazole or other azoles. Topical enilconazole twice a week for 3 weeks is recommended (Bourdeau, 2000).

All bedding, cages and other potential sources of infection should be disinfected with an antimycotic disinfectant or destroyed.

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