

Advances in the understanding of fleas and their control

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Figure 1 An adult *Ctenocephalides felis felis*.

KEY POINTS

- *Ctenocephalides felis felis* is the most commonly reported flea found on dogs and cats.
- Environmental conditions are extremely important in the development of the cat flea.
- The pupa and the pre-emerged adult within the pupal case are highly resistant to control programs.
- A combination of topical and environmental treatments will achieve the best control.
- Flea bite hypersensitivity makes effective flea control mandatory. Some additional anti-inflammatory treatment is usually necessary.

INTRODUCTION

This article puts into context recent advances in understanding and controlling fleas and flea bite hypersensitivity. The progress made in flea control may make clinicians believe that they have it taped – by looking toward the future they may be warned against complacency.

THE FLEA

Species of flea

The species of flea reported most commonly on cats and dogs throughout the world is the so-called cat flea, *Ctenocephalides felis felis* (*C. f. felis*), one of four sub-species of *C. felis* believed to have originated in Africa. The spread of *C. f. felis* has been assisted by the movement of pets around the world. It is a fairly robust species and, although its original host was the cat, it is not very host-specific. For example, where *C. f. felis* has encountered the original species found

on dogs (*Ctenocephalides canis*) it appears to have displaced it. This is probably because *C. canis* is more host-specific and more particular in its environmental requirements than *C. f. felis*. Nonetheless, *C. canis* remains the predominant species found on dogs in countries such as Greece, New Zealand and Ireland, and may be found on kennelled dogs or those in rural areas of the UK.

Other species of fleas, apart from *C. felis*, are less commonly identified on cats and dog, although in some parts of the USA *Pulex irritans* is often found on dogs. *P. irritans* is often called the 'human' flea, but in fact it is a fairly cosmopolitan species that originated on pigs (1). Other species of flea may be found on dogs or cats as a result of their hunting behavior. However, the bulk of recent research has been on *C. f. felis*, (Figure 1), and this is the flea that this article will concentrate on.

Biology of *C. f. felis*

Adult fleas are permanent residents on their animal host and female *C. f. felis* fleas lay their eggs on the host. Once an adult flea has located a host, it jumps onto the animal and begins feeding on blood almost immediately. When a female has taken an initial feed, mating occurs, after which egg-laying begins. It has been shown that some strains of flea will begin egg-laying within 24 hours of host location (2). This observation has implications for flea control that will be discussed later.

Female fleas can lay up to 46 eggs per day, each female continuing to lay eggs daily until her demise (3). Adult fleas have survived on cats for up to 113 days (3), in cases where the host was prevented from scratching and grooming. However, life expectancy for the majority of fleas is probably only about one or two weeks, as many are removed by grooming (4). Hinkle *et al* found that the proportion of fleas removed by grooming varied from cat to cat (4). The most effective groomer removed 17.6% of its flea burden daily, while the poorest removed only 4.1%.

Female fleas consume considerably more blood than males and the blood passed in their feces is virtually unchanged. It is believed



that the female flea produces copious feces as a source of nutrition for the young flea larvae (5). Flea feces, together with the smooth-shelled eggs, fall out of the host pelage into the surrounding environment. Both tend to accumulate in the areas where the host lies, thus ensuring that a host is likely to be available for the adult flea when it has emerged from its pupal cocoon.

Once eggs have fallen from the host's coat, they are in an environment where temperature and humidity may fluctuate much more than on the host animal. The development of the flea, from egg to adult, depends totally on environmental conditions. For example, at 24 °C and 78% relative humidity, the period between the egg being laid and the emergence of the adult was 17–22 days for females and 20–26 days for males (6). Within tolerance limits, at lower temperatures development will still take place, although it is slower. The environmental tolerance limits of *C. f. felis* are shown in

Table 1.

Once hatched, the developing larvae undergo three molts. During this time they search their local environment for food and move away from light (negative phototrophism) and towards the ground (positive geotrophism). This means that when they begin to pupate they are often located in extremely inaccessible cracks or in the base of carpets. Such locations offer the pupae and pre-emergent adult good protection against any insecticides that may be present in the environment (7). Once pupation is complete, the adult flea may emerge from the pupal cocoon immediately or may choose to remain as a 'pre-emerged' adult for days, weeks, or even months. Pupae and pre-emerged adults are protected from most control methods and may well survive environmental treatment regimens only to emerge as their effect wanes; this has been termed the 'pupal window'. Stimuli for the emergence of pre-emerged adults include pressure and warmth (8).

WHY CONTROL FLEAS?

Fleas are a pest to animals and man. Allergy to fleas, so-called flea bite hypersensitivity (FBH), is a major cause of dermatitis in cats and dogs. A heavy flea burden can cause anemia (see the case study), and fleas may be involved in the transmission of endoparasites such as the tapeworm *Dipylidium caninum*, and possibly of other diseases (9). The cat flea is not highly host-specific and will readily jump onto humans in its search for a suitable host. In homes where there is a large emergent flea problem, human members of the household can be severely bitten. Following exposure to flea bites, a few people may develop severe allergic reactions to subsequent bites.

DETERMINING THE PRESENCE OF FLEAS

Overt infestation with fleas is uncommon in adult, healthy animals. In many cases the grooming activity of the cat or dog removes the fleas quite rapidly, making diagnosis difficult. Noting the presence of flea feces in coat combings (Figure 2) is often a reliable diagnostic tool. In some cases zoonotic lesions may be reported, particularly on the lower legs (Figure 3). The presence of gravid segments of tapeworm may be noted on the perineum (or on carpets), suggesting flea or louse infestation.

Diagnosis is even more difficult if FBH is present (Figures 4 to 7) because the pruritus, and resultant over-grooming, quickly removes the evidence of infestation. It may be necessary to examine the in-contact, but apparently unaffected, animals in order to confirm the presence of fleas in the household.

Table 1
Environmental tolerance limits for immature *Ctenocephalides f. felis* (8)

<i>Minimum temperatures</i>	
3 °C	for 5 days lethal to eggs and pupae
10 °C	first instar larvae die
13 °C	development of all stages occurs
<i>Maximum temperatures</i>	
35 °C	pupae develop but adults fail to emerge
<i>Moisture</i>	
Less than 33%	relative humidity larvae die
95% relative humidity	or more allows fungal overgrowth and subsequent death of larvae
< or > 10%	soil moisture decrease larval survival



Figure 2 The presence of flea feces in coat combings may be better appreciated if they are placed upon damp cotton wool or tissue paper. The blood then becomes readily apparent.



Figure 3 Erythematous papules on the lower legs of this woman are the result of flea bites.

ADVANCES IN TREATMENT AND CONTROL

Flea populations may be controlled by chemical or non-chemical means. Non-chemical measures include the grooming of pets and vacuum cleaning the environment. These are normally regarded as beneficial ancillary methods of flea control. Currently, chemicals are the main means of limiting flea populations; these include insecticides and insect growth regulators (IGRs) (Table 2).

Insect growth regulators

There are two IGR groups: the juvenile hormone analogs and the chitin synthesis inhibitors. The individual compounds are listed in Table 2. Methoprene is probably the best-known juvenile hormone analog and it is structurally similar to natural juvenile hormone. It affects flea development at a number of stages (Table 3). Olsen (10) reported that a 0.3% methoprene spray applied to cats at a dose rate of 10.4 mg/kg prevented the emergence of adults from eggs laid on cats for 42 days after application. However, to date it has most commonly been formulated as an environmental treatment.

An insecticide such as permethrin, is often added to methoprene formulations for environmental application. This is because pupae and pre-emerged adults are not susceptible to methoprene treatment. The success of such combinations depends on:

- Degree of access to all areas of flea development. Immature stages that are susceptible to the active compound *in vitro* may be protected from treatments applied into the environment.
- Environmental temperature. The speed of development in a cool environment may be so slow that adult fleas emerge only when insecticidal activity has waned.



Figures 4 and 5 Alopecia on the dorsum commonly accompanies flea infestation and flea bite hypersensitivity. In the Siamese cat in Figure 4 the regrowing hair is darker than normal.



Figure 6 Symmetrical alopecia may be quite extensive in the cat. Here it affects the perineum and ventral abdomen.

Figure 7 Some cats with flea bite hypersensitivity may exhibit a papulocrustous dermatitis in association with alopecia.

- Duration of action of the insecticide. The effect of a short-acting insecticidal component may wane while fleas that were pupae or pre-emerged adults at the time of treatment are still emerging.

Pyriproxyfen and fenoxycarb appear to act as juvenile hormone analogs but are not structurally related to juvenile hormone. Pyriproxyfen has been shown to prevent flea development for up to seven weeks after spot-on application to cats (11).

Lufenuron is a chitin synthesis inhibitor that has been developed as a flea control agent. The chemical was originally available as an oral tablet, or suspension, for monthly administration. Recently, a depot formulation for subcutaneous injection in cats has been reported to control fleas for six months (12). As with other IGRs, when lufenuron is used as a sole agent one would anticipate a lag period before complete flea control is achieved. For this reason, it is recommended that treatment is commenced before the 'flea season' begins.

Both cyromazine and diflubenzuron have been shown to control fleas. For example, Shipstone *et al* (13) found that cyromazine, administered daily to dogs at 10 mg/kg alongside a heartworm prophylactic treatment, substantially reduced flea burdens 12 weeks after treatment began. Henderson and Foil (14) found that the activity of diflubenzuron, applied to a carpet at 53 mg/m², prevented adult flea development for 12 months.

Insecticides

The major groups of insecticide and representatives of each group are shown in **Table 2**. The older products have been reviewed – for example, by Kwochka (15).

In recent years two major new active ingredients for flea control have become available – fipronil and imidacloprid. Both products are available as spot-on formulations and fipronil is also available as a pump spray.

Table 2
Groups of flea control actives

Insecticidal groups	Examples of compounds used
Carbamates	Propoxur
Organophosphates	Cythioate Diazinon Fenthion
Pyrethroids	Pyrethrins Fenvalerate Permethrin
Phenyl pyrazoles	Fipronil
Chloronicotinyl guanidine	Imidacloprid
Borates	Sodium polyborate (*)
Insect growth regulators (IGRs) (†)	
Juvenile hormone analogs	Methoprene Pyriproxyfen Fenoxycarb
Chitin synthesis inhibitors	Cyromazine Lufenuron Diflubenzuron

(*) Used for control of environmental stages only.

(†) Used to prevent fertile egg production or to control developing stages in the environment.

Does not include older compounds, such as organochlorides, organobromides, and rotenone.

Table 3
Effects of individual insect growth regulators (IGRs) following application to the animal or to the environment

IGR	Application to environment	Application to animal
Methoprene	Prolongs larval instars and reduces pupation	Prevents fertile egg-laying
Fenoxycarb	Treatment of eggs prevents hatch or causes death of young larvae	
Pyriproxyfen	Inhibits larval development	Eggs collapse as they contain no yolk. A spot-on prevented fertile egg-laying for seven weeks
Lufenuron		Eggs fail to hatch or produce small larvae that die
Diflubenzuron	Death of larvae at each molt – the higher the dose the earlier the effect. Inhibits cocoon formation	
Cyromazine	Elongated adults, prevents normal pupation	

Fipronil is a phenylpyrazole and it is the sole member of that group to have been developed as a flea control product. In the insect, fipronil affects the gating of GABA-mediated chloride channels, where it appears to act as a GABA antagonist (16). In trials, good knockdown efficacy has been described 24 hours after treatment of cats and dogs, with both the spray and spot-on formulations (17–19). Once applied, fipronil appears to bind to sebaceous material on the host's skin (20) and so provides prolonged protection against subsequent flea challenge. In the UK, the spray formulation is claimed to protect against fleas for up to three months in dogs and two months in cats while the spot-on formulation is claimed to be effective for up to two months in dogs and five weeks in cats. Efficacy appears to be well maintained through washing or bathing of dogs (19, 21, 22) though neither activity is recommended one to two days before or after treatment. Monthly fipronil spot-on treatment successfully controlled a flea infestation in cats in a simulated infested home environment (23).

Imidacloprid is a member of the chloro-nicotinyl guanidines and is formulated as a spot-on preparation for monthly treatment to control fleas on cats and dogs. Efficacy against challenge was maintained at 95.1% twenty-eight days after treatment of dogs and at 95.7% twenty-eight days after treatment of cats (24). Monthly imidacloprid treatment of cats in a simulated, contaminated home environment was found to control the flea infestation completely (25).

Methods of application

Generally, the easier the mode of application the more likely that client compliance with the treatment regimen is going to be adequate (2).

CREATION OF A CONTROL PROGRAM

There are a number of different circumstances where flea control may be sought and, as owners become more aware, prophylactic control may be requested more frequently. A veterinarian is therefore likely to have several 'off the peg' regimens to suit the common situations encountered.

In a situation where there is an established flea population on an animal there are two main aims:

- To break the life cycle, thereby controlling the existing problem.
- To keep it broken – i.e., to prevent the problem recurring.

The flea's life cycle is a simple one, so breaking it at any point should stop its development. In the past it has often been perceived that it is necessary to break it at two points (by killing adults and environmental stages) in order to obtain control. There may be a number of reasons for the apparent inability of a single treatment to control the problem (Table 4). One important factor is the ability of some strains of flea to lay eggs within 24 hours of arrival on a host (2). This means that an insecticide must kill all fleas in less than 24 hours to ensure that no eggs are produced. The speed of kill of an insecticide may decline with time after application, so, while there may be no viable eggs laid immediately after treatment, after a few weeks a small number of viable eggs may be produced (2).

The quickest control of a flea population will probably be effected with a dual approach to the problem. However, once the initial problem is under control, it may be possible to prevent recurrence with the repeated use of one treatment. Non-chemical methods of control, including vacuum cleaning, washing of bedding, and combing of the animal, should be included in the control program. Combing has the additional benefit of providing owners with feedback on the effectiveness of their control measures. Combing should be carried out for several minutes and should include all parts of the body, but particularly the neck area and behind the ears.

Table 4

Possible reasons for the apparent failure of flea control programs

- Reduced efficacy of treatment prior to the retreatment date, allowing fleas that land on the host at this time to lay viable eggs
- Ability of fleas to lay viable eggs prior to insecticide killing the flea
- Lag period after the instigation of an IGR program
- Failure to treat all animals in a household
- Failure to consider all of the animals' habitats – e.g., another home visited regularly, the car
- An external source of fleas (may be an animal visitor to the household)
- Source of reinfestation from the household environment because of immature stages that were not reached by environmental application of insecticide and/or IGR
- Pupae or pre-emerged adults emerged after environmentally applied insecticide had worn off or were unaffected by IGR application

In some parts of the world, such as eastern Australia and Florida, fleas may breed outdoors throughout the year, so outdoor as well as indoor control is regularly considered. For example, in the USA, a biological flea control using a preparation of *Steinernema carpocapsae* is available. This is a nematode that naturally acts as a parasite on developing fleas. Studies have demonstrated that it is an effective method of control, particularly on gravel surfaces (26). Inoculation of the ground may have to be repeated at intervals as the nematode population may decline once the environmental flea population has been reduced. Insecticidal and/or IGR preparations for outdoor use may also be available. However, methoprene degrades quite rapidly in sunlight and is thus not suitable for outdoor application.

In other areas there is little information about the relative importance of the outdoor environment as a contributor to flea reinfestation. In temperate climates, such as that in the UK, the summer may provide suitable microclimates for flea development, but survival over the winter is unlikely as conditions are well outside the flea's environmental tolerance (Table 1). Although there may not be specific licensed outdoor treatments in these areas some topical products may affect the environmental flea population. It has been shown, for example, that a topical application of either fipronil or imidacloprid has an insecticidal effect (for example, where the animal lies), thus offering environmental control. Similarly, lufenuron should help to prevent significant outdoor flea replication, as it prevents fleas on the animal from laying fertile eggs and flea feces falling into the environment and ingested by larvae will prevent normal larval development. The degree of success depends on the extent to which other animals, especially cats and dogs, in a local area contribute to the outside environmental flea population.

RESISTANCE

Resistance has been defined as the genetic development by a target population of the ability to tolerate a dose of toxicant that would prove lethal to the majority of individuals in a normal population of the same species (27). It is important that this is clearly distinguished from ineffectiveness caused by inappropriate application. To achieve this distinction it may be necessary to perform a careful investigation of cases of apparent treatment failure.

True resistance to an insecticide or other chemical may become

apparent when a product that previously controlled fleas fails to do so, despite appropriate application. There have been a number of reports of flea strains that are resistant to one or more insecticides. Most resistant strains have been reported in, or originate from, areas such as Florida, where the indoor and outdoor use of insecticides for pest control is commonplace throughout the year (7, 28).

At present, the owner's selection of an active ingredient for flea control is usually spontaneous and depends on unrelated factors such as cost, availability, and ease of compliance. Owners frequently fail to carry out a logical strategy to prevent, or delay, the onset of resistance. This partly reflects a lack of knowledge of the factors responsible for resistance in fleas. At present, guidelines are based on evidence gleaned from an understanding of resistance to insecticides in other species, such as mosquitoes. This evidence suggests that some form of alternation of active ingredients is advisable. The combined use of two products with different modes of action may be another method of delaying the onset of resistance.

CONTROL OF FBH

Ideally, animals suffering from FBH would have their condition reversed immunologically, so that a chance exposure to fleas would no longer have the potential to induce severe skin disease and irritation. Unfortunately, there has been little success, despite a number of attempts, using different treatment schedules, at desensitizing cats or dogs. However, very recently Kwochka *et al* reported the first apparently successful desensitization of dogs (29). Using a rush immunotherapy schedule and flea salivary antigen, they were able to show significant improvement in the animals that received the treatment schedule.

Until such therapy becomes refined and widely available, treatment of animals with FBH relies primarily on eliminating the source of allergen by removal of the flea challenge. Secondary treatment with antiinflammatory agents (such as glucocorticoids) may be necessary, either to bring the initial signs under control or as a long-term adjunct to flea control. The use of antiinflammatory agents will depend on the severity of the condition and the level of flea control that the animal's owners are willing, and able, to undertake.

Glucocorticoids should not be used as the sole treatment and a comprehensive approach to flea control for the animal with FBH is appropriate. Recent studies have examined the efficacy of repeated treatment regimens in preventing the recurrence of clinical FBH and/or reducing the clinical signs associated with the condition. Results suggest that a fipronil regimen (30, 31) or the use of lufenuron (32) may reduce the flea burden on the animals over time and so improve the animal's clinical condition without recourse to glucocorticoids.

Flea control is especially important in the short term, until the flea population is brought under control. The aim of initial control should be to kill fleas already on the animal and protect it from fleas that land on it over the following few weeks, so allowing its existing skin lesions to heal. The developing flea challenge in the environment should be tackled by vacuum cleaning and suitable environmental treatment. The aim should be to control the skin problem using the minimum number of chemicals and treatments, as this is likely to maximize client compliance.

Long-term monitoring of the effectiveness of the control program may be carried out by regular flea combing, which may allow early identification of a control breakdown before clinical signs have reappeared. Owner awareness of normal and increased levels of scratching and licking may also allow clinical disease to be caught at an early stage. Studies of the effectiveness of treatments may now include video recordings of an animal's behavior so that episodes of

Case Study

A nine-year-old Collie (below) was presented to a veterinary surgeon in late August in southern England as the owners were concerned about it being lethargic. The veterinary surgeon noticed two things in particular during his initial clinical examination: fleas and extremely pale mucous membranes. A blood sample was taken, the dog was treated with flea spray and the owners were provided with environmental treatment. The clinician commented that there was a large, though not enormous, number of fleas. The results of the initial hematology profile and later follow-ups are shown below:

Blood Parameter	August 29	September 8	October 6	Reference Range
WBC ($\times 10^9/l$)	8.5	7.1	10.7	6.0–15.0
RBC ($\times 10^{12}/l$)	2.76	4.93	7.08	5.0–8.50
Hemoglobin (g/dl)	2.8	7.2	11.8	12.0–18.0
PCV (%)	14.2	29.7	41.1	37.0–55.0
MCV (fl)	51.4	60.2	58.1	60.0–77.0
MCH (pg)	10.1	14.6	16.7	19.0–23.0
MCHC (g/dl)	19.7	24.2	28.7	31.0–34.0

Diagnosis: anemia due to exsanguination by fleas.

Outcome: following flea control, the anemia resolved.



The dog featured in the case study, photographed during the recovery phase.

scratching and licking can be counted (29).

Animals with FBH benefit from an effective repellent as this may prevent, or reduce, flea feeding on an individual. Recent studies reported by Ascher *et al* suggest that a combined permethrin (2%) and pyriproxyfen (0.02%) spray has both an anti-feeding effect and a rapid knockdown after flea challenge (33).

FUTURE DEVELOPMENTS IN FLEA CONTROL

At present, those practicing flea control are going through something of a honeymoon period. The development of two new unrelated chemicals, together with other developments in flea control, provides a range of choice not previously available. The size of the flea control market may offer an incentive to produce more, and possibly better, products but, equally, the quality of the products now available may inhibit companies from undertaking the expense of new drug development.

Coordinated flea and worm programs – such as the combination of milbemycin and lufenuron now introduced into the USA, Australia, and Italy – may be further developed. Single formulations with endectocidal activity may become available for the treatment of small animals. One such avermectin derivative has reportedly successfully controlled fleas in cats and dogs (34).

As with other products, the flea control market is now global.



Fipronil, for example, is licensed in 60 countries worldwide. This is likely to become the norm, as it may be unviable for companies to develop a product for a local market. Furthermore, mutual recognition of both test and trial data will tend to encourage this process. These developments bring both opportunities and, perhaps, problems. The income from a major product can provide investment for further research, but this is only valuable if such research is perceived as credible when sponsored by the manufacturer. Globally active ingredients have the potential to create global resistance,

again highlighting the need for rational flea control.

The hope is that integrated programs combining chemical and non-chemical methods of flea control will be developed. For example, we may see the commercial introduction of an effective flea trap to remove emergent fleas from the environment.

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