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UPDATES IN DERMATOLOGY

Canine sebaceous adenitis – Canine pruritus: causes and therapies – Canine pyoderma: a tiered approach – Managing skin disease with fluorescence biomodulation – Chronic canine otitis: prevention is better than cure – Demystifying the biofilm in canine otitis – The skin barrier in canine atopic dermatitis – How I approach... feline atopic skin syndrome

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THE SKIN – MUCH MORE THAN JUST A SURFACE CASING

"Wisdom is not a product of schooling but of the lifelong attempt to acquire it" **– Albert Einstein**

The debate amongst medical historians as to who can claim to be the first human dermatologist is not an easy one to untangle. One candidate is Andries van Wezel, a 16th century Flemish anatomist who, although not a dedicated skin specialist, was apparently the first to analyze the skin properly, identifying its constituent layers and describing its different components. He went on to write a textbook, *De Humani Corporis Fabrica Libri Septem*, and was perhaps the first to lay to rest the long-held belief – which stretched back to the ancient civilizations – that the skin was no more than "a surface casing that comes off easily". (Indeed, the Greek word *derma,* for instance, originally referred equally to an animal hide or the skin of a vegetable.) Another candidate is Daniel Turner, a London physician who published a dermatology textbook entitled *De Morbis Cutaneis*. It first appeared in 1714 and was so successful that it went through several editions in various languages. Then there is Jean-Louis-Marc Alibert, whose work amongst patients with various skin disorders in a Parisian hospital led him to develop a rudimentary classification system for dermatological problems. Whilst his system would not stand up to modern scrutiny, it did have a basic logic to it, and he too produced a classic textbook, namely *Descriptions des Maladies de la Peau*.

The debate on who can be identified as the original veterinary dermatologist is, however, a great deal easier. In fact, it is only some 120 years ago – 1903 to be exact – that the first book on the subject was published. *Hautkrankheiten bei Haustieren* was authored by Dr. Hugo Schindelka, who was based at Vienna's Veterinary School, and basically established veterinary dermatology as a discipline in its own right.

But all these individuals – and more – have at least one thing in common – namely, their desire to develop our comprehension of skin problems and to pass that knowledge to others. A century on, and the field continues to expand in all directions, whether that be in disease identification, diagnostic methods, or new treatment options. This modest publication takes its place amongst many dermatological textbooks and journals, all dedicated to further progressing the treatment of skin disorders in order to benefit the patients we treat on a daily basis.

Ewan McNEILL
Editor-in-chief, *Veterinary Focus*

In this issue of *Veterinary Focus*

CANINE SEBACEOUS ADENITIS

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Dr. Perry completed his veterinary studies at the Hebrew University's Faculty of Veterinary Medicine in 2011, followed by an internship at the same institution. After four years working as a general practitioner, he pursued his dermatology residency, achieving board certification in 2023. Dr. Perry offers dermatological consultation in private clinics and referral centers across Israel, and actively contributes to the training of veterinary students in the Dermatology Department at the University Veterinary Hospital.

What is sebaceous adenitis? Many clinicians are unaware of this condition in dogs, but this article details all you need to know.

KEY POINTS

1. Canine sebaceous adenitis is a rare skin disorder characterized by inflammation and destruction of the sebaceous glands.
2. Definitive diagnosis is based on a combination of history, characteristic clinical presentation and histopathology.
3. Clinical signs may vary by breed but often include hair loss, erythema, and the presence of follicular casts, with more severe cases leading to secondary infections.
4. Treatment options include both systemic and topical therapies, but the prognosis varies based on severity and response to treatment.

Introduction

Sebaceous adenitis in dogs is a distinctive dermatological disorder characterized by an inflammatory pathogenesis that primarily affecting the sebaceous glands, resulting in their degeneration (1). Practicing veterinarians worldwide will encounter cases, and it is crucial to have a comprehensive understanding of this condition to provide optimal care. This article will explore sebaceous adenitis, including its clinical features, diagnosis, available treatments and prognosis, with the aim of assisting veterinarians in managing this challenging condition.

Etiology

The term "sebaceous adenitis" refers to the inflammation and subsequent destruction of the sebaceous glands; these are responsible for producing sebum, an oily substance that helps keep the skin and coat healthy (1,2). The exact etiology of canine sebaceous adenitis is not fully understood, but it is believed to have a multifactorial origin. Genetic predisposition is strongly suspected to play a significant role in the development of this condition (1). In some breeds, such as the Akita and Poodle, it is assumed that sebaceous adenitis follows an autosomal recessive mode, and ongoing studies are seeking to identify specific genetic markers and mutations that may contribute to susceptibility (3-5).

In addition to genetic factors, immune system dysfunction is believed to be a major contributor to the etiology (1). Glandular destruction is linked to a cell-mediated immunologic response targeting the glands. Immunohistologic analysis of samples from affected individuals reveals the presence of dendritic antigen-presenting cells and T-cells concentrated in the middle part of the follicle, extending into the

sebaceous duct (6). This observation strongly suggests an immune-mediated pathogenesis, and the positive response often noted to treatment with cyclosporine further supports this theory.

Further possible contributors to the etiology involve anomalies in lipid metabolism, defective lipid storage, or abnormalities in keratinization, which can lead to obstruction of sebaceous ducts and inflammation caused by lipid leakage (1). Moreover, various environmental factors, including stressful events like illness, general anesthesia, surgery and exposure to heat, may initiate or exacerbate the condition (1,3). Additionally, exposure to sunlight (photoaggravation) can further worsen the disease (1). A comprehensive understanding of these potential factors is essential in the diagnosis and management of sebaceous adenitis.

Signalment

Canine sebaceous adenitis is a rare and complex dermatological condition that primarily affects certain breeds such as the Standard Poodle, Akita, Samoyed, Havanese and Vizsla, although it can occur in mixed breeds as well (1,7). The disease tends to appear in young adult to middle aged dogs, although it can be seen at any age. No sex predilection has been noted (1,7).

Clinical appearance

The clinical signs of sebaceous adenitis and their severity can vary significantly among individual dogs, and are also influenced by the breed (8). In short-haired breeds, such as Vizslas, Miniature Pinschers and Dachshunds, clinical skin lesions typically begin with annular patterns characterized by hair loss and erythema. These lesions often exhibit fine, white, and non-adherent scales **(Figure 1)**. Over time they may enlarge peripherally, taking on a polycyclic appearance or coalescing into larger affected areas **(Figure 2)** (1,6).

Skin lesions associated with sebaceous adenitis often display a symmetrical pattern, and typically affect specific areas of the body. Commonly affected regions include the pinnae **(Figure 3)**, face **(Figure 4)**, head and dorsal trunk (1,9). In more severe cases, external ear inflammation (otitis externa) may be observed, and ulcerative lesions in the pinnae have been reported (10). Additionally, a recent report has indicated blepharitis and meibomian gland dysfunction in a dog affected by sebaceous adenitis (11).

One characteristic sign of sebaceous adenitis is the presence of follicular casts, which can vary in their visibility. These casts are characterized by groups of hairs matting together due to a sheath of keratin debris **(Figure 5 and 6)**. This debris remains attached to the hair above the follicular ostia. While this feature is not entirely specific, it can be an invaluable aid in diagnosing the condition (3,12).

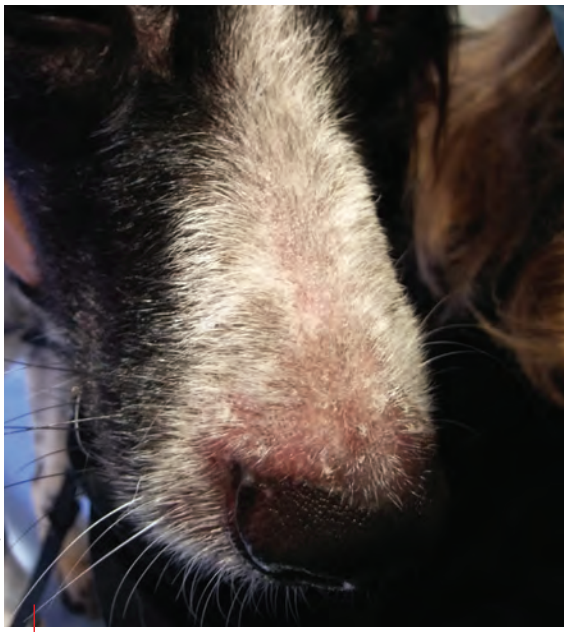

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Figure 1. Exfoliative dermatitis with whitish adherent scales, mild erythema and hypotrichosis on the muzzle and periocular region of a dog with sebaceous adenitis.

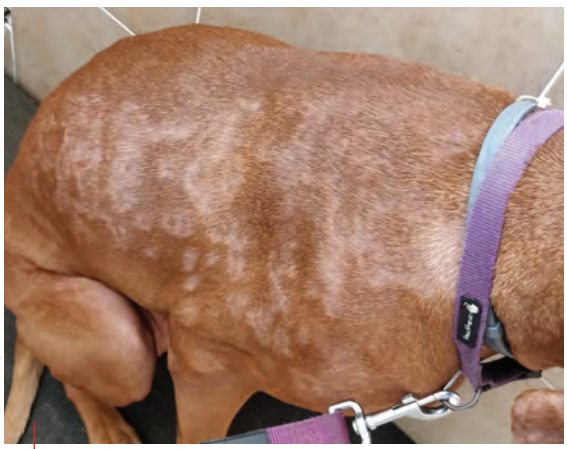

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Figure 2. Annular to polycyclic areas of alopecia over the trunk of a Vizsla with sebaceous adenitis.

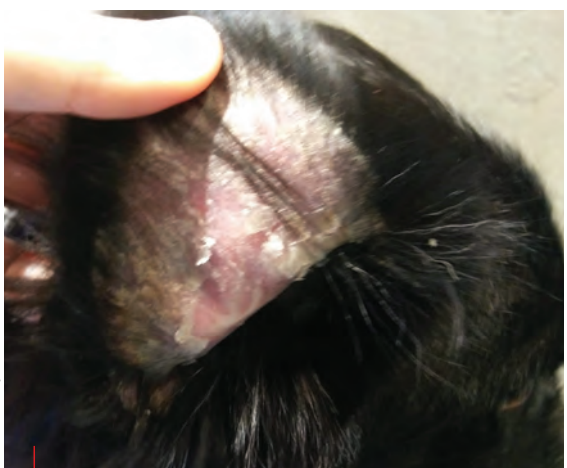

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Figure 3. Whitish adherent scales on the concave surface of the pinna of a dog with sebaceous adenitis.

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Figure 4. Alopecia with whitish powdery scales on the face of a Vizsla dog with sebaceous adenitis.

While varying degrees of pruritus may be observed in affected dogs, it is typically not regarded as a defining characteristic of the condition unless secondary pyoderma is also present (2,7). Nonetheless, it is noteworthy that the author has seen instances of canine sebaceous adenitis with pruritus even in the absence of secondary pyoderma. Moreover, a review of medical records for 24 dogs with sebaceous adenitis found that 19 of them exhibited pruritus, but only eight had concurrent superficial pyoderma (13).

For long-haired breeds such as the Akita, Poodle and Samoyed, sebaceous adenitis can present with similar signs to their short-haired counterparts. These breeds may experience severe matting and clumping of fur due to impaired sebum production. This is more pronounced than in short-haired breeds, and typically occurs in the head, pinnae, neck, back and tail regions. Hair loss with or without erythema is common, leading to noticeable bald spots, particularly on the back, tail, and neck **(Figures 7, 8 and 9)** (7,12).

In long-haired breeds color changes may also be observed, along with alterations in hair texture from curly to wavy or straight. These changes may progress to poor, dull, and brittle hairs. The accumulation of dead skin cells and matted hair in these regions can create an environment conducive to secondary bacterial skin infections, leading to discomfort and pruritus in affected dogs (1,7).

Diagnosis

When diagnosing sebaceous adenitis, it is crucial to differentiate it from other skin diseases that can present with similar clinical signs. These potential differentials include atopic dermatitis, leishmaniasis (in endemic areas), and infectious conditions such as dermatophytosis, demodicosis, and bacterial folliculitis. Immune-mediated skin disorders like pemphigus foliaceous and cutaneous lupus erythematosus should also be considered. Furthermore, hormonal imbalances, nutritional deficiencies (such as zinc or fatty acid deficiencies) and nutritionally responsive conditions (such as zinc-responsive dermatosis or vitamin A-responsive dermatosis) can also mimic sebaceous adenitis (1,7).

Due to this array of potential differentials and the varied clinical signs associated with sebaceous adenitis, a comprehensive approach is imperative for confirming the diagnosis. A thorough clinical examination is the first step, looking for characteristic signs such as annular lesions, hair loss, erythema, and the presence of follicular casts. The distribution of skin lesions and their symmetry is also important and indicative of the condition.

A trichogram, which entails plucking hairs from the affected area, can be conducted to detect hair shaft abnormalities. In cases of sebaceous adenitis these hairs may exhibit a distinctive waxy appearance,

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Figure 5. Hairs pulled from a dog with sebaceous adenitis, with their roots filled with keratin (follicular casts).

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Figure 6. A close-up of the hairs of a dog with sebaceous adenitis. Follicular casting can be observed at the opening of the hair follicles.

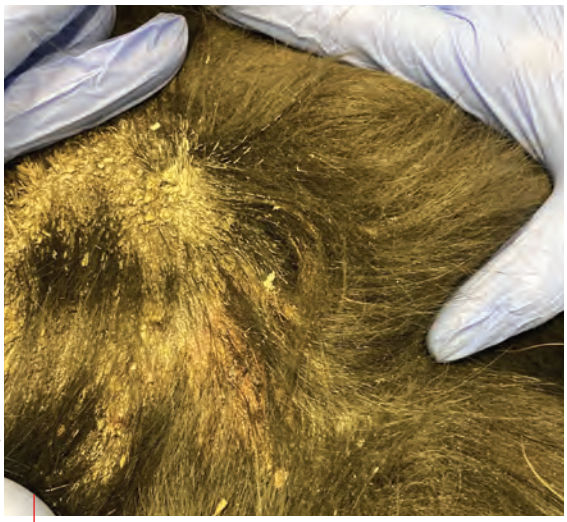

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Figure 7. Scaling and follicular casting on the dorsal trunk of a dog with sebaceous adenitis.

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Figure 8. Severe hair loss on trunk of a dog with sebaceous adenitis.

with their roots possibly filled with keratin (follicular casts). Furthermore, when combined with skin scraping, this procedure can assist in ruling out follicular parasites such as *Demodex* mites.

Cytological examination of skin lesions can reveal any secondary infections or inflammatory cells present in the affected areas. This information can be valuable for assessing the extent of the condition and planning treatment. In some cases, blood samples may help rule out underlying medical conditions that can mimic the signs of sebaceous adenitis (*e.g.*, testing for leishmaniasis in endemic areas, or hormonal imbalances).

A skin biopsy is often recommended to confirm the diagnosis definitively. The histopathologic features of sebaceous adenitis are highly variable but typically consist of diffuse absence of sebaceous glands and isthmus perifollicular granulomatous to pyogranulomatous inflammation. Lymphocytes, mast cells, plasma cells and eosinophils can also compose the dermal infiltrate that targets the sebaceous gland. Additional features may include orthokeratotic hyperkeratosis, follicular keratosis, and acanthosis **(Figure 10)** (2,14,15).

Sebaceous adenitis may occur either as an idiopathic condition or as a secondary manifestation of other dermal inflammatory disorders, such as canine leishmaniasis, which is considered a reasonable differential diagnosis in endemic areas. Histologically, both canine leishmaniasis and idiopathic sebaceous adenitis can exhibit granulomatous or pyogranulomatous inflammation of the sebaceous glands; however, a recent report found that the two conditions can be differentiated histopathologically (14). According to the study, sebaceous adenitis in cases of leishmaniasis were histologically characterized by nodular to diffuse dermal infiltrate in addition to epidermal and subepidermal lesions and absence of marked hyperkeratosis and follicular keratosis, whereas in idiopathic sebaceous adenitis inflammation was generally restricted to the sebaceous glands, and hyperkeratosis and follicular keratosis were present.

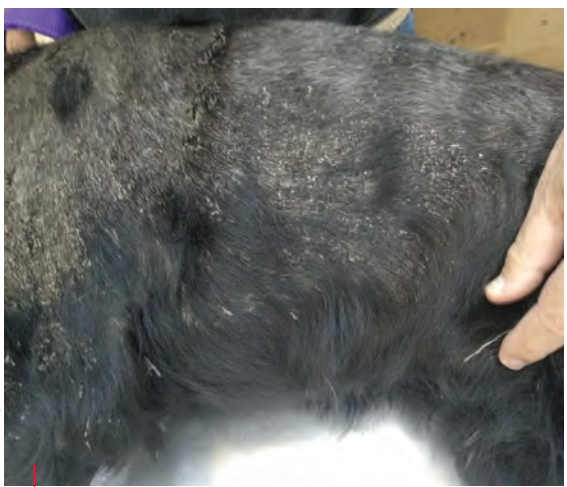

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Figure 9. Alopecia, scaling and follicular casting on trunk of a Schnauzer dog with sebaceous adenitis.

Treatment options

Managing sebaceous adenitis in dogs necessitates a comprehensive approach; the primary objectives of treatment are to reduce the accumulation of excess scales, enhance the quality of the hair coat, and mitigate inflammation and damage to the sebaceous glands. This multifaceted approach helps manage the condition effectively and improve the dog's overall comfort and appearance. Treatment options encompass both systemic and topical approaches, and the choice depends on the severity of the condition and individual patient considerations. It is important to note that there is no one-size-fits-all approach, and that regular follow-ups and adjustments to the initial treatment plan are often necessary to achieve the best outcomes.

Cyclosporine, an immunosuppressive medication, is a common choice for managing sebaceous adenitis. It plays a crucial role in modulating the

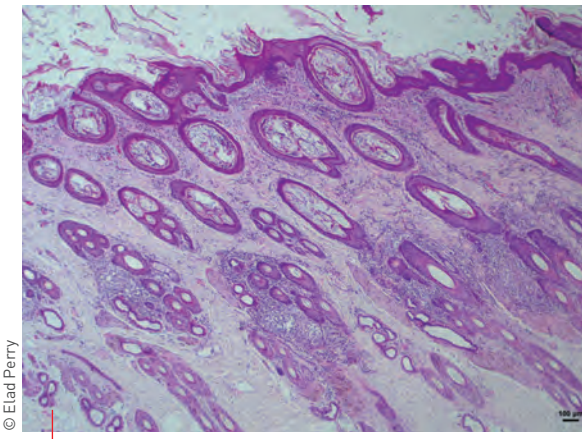

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Figure 10. Photomicrograph of haired skin of a dog with sebaceous adenitis. Low magnification reveals moderate to severe infiltration in the isthmus area of the hair follicle, absence of sebaceous glands and hyperkeratosis of the epidermis with follicular keratosis. Hematoxylin and eosin stain; scale bar 100 µm.

abnormal immune response that triggers the condition, and it can also induce hypertrichosis, potentially reducing the plugging of the follicular infundibulum with keratinaceous material in affected dogs. A dosage of 5 mg/kg/day has been shown to effectively reduce the inflammation associated with sebaceous adenitis (16), and in most cases cyclosporine can be tapered gradually once clinical signs have resolved. However, it is crucial to emphasize that long-term treatment is essential for controlling the condition (16).

Notably, combining topical therapy with cyclosporine can produce a synergistic benefit, positively impacting both scaling and alopecia while also reducing inflammation of the sebaceous glands (17). Furthermore, cyclosporine may promote better regeneration of the glands compared to topical treatment alone (17).

"Managing sebaceous adenitis in dogs necessitates a comprehensive approach; the primary objectives of treatment are to reduce the accumulation of excess scales, enhance the quality of the hair coat, and mitigate inflammation and damage to the sebaceous glands."

Elad Perry

Essential fatty acids (EFAs), whether administered systemically or applied topically, have demonstrated effectiveness in certain patients (18). Given their generally mild side effects, EFAs are frequently considered as an initial option, either independently or in combination with immunosuppressive therapies.

Vitamin A (retinol) and synthetic retinoids, which are derivatives of vitamin A, have been reported as a treatment of sebaceous adenitis, albeit with varying degrees of success (13,19). These compounds, in addition to their anti-inflammatory properties, play a crucial role in keratinocyte proliferation and differentiation, thereby normalizing the keratinization process and promoting skin health (20). Retinoids are less favored by clinicians due to the low availability of the drug and its adverse side effects, which include keratoconjunctivitis sicca, teratogenicity, gastrointestinal upset, and hepatotoxicity. Careful monitoring is essential to detect any of these side effects in treated patients (20).

Anecdotal reports suggest that a combination of oral tetracycline and niacinamide may yield positive results in some cases. Dogs weighing less than 25 kg typically receive both medications at a dosage of 250 mg q8h, while dogs above this weight are treated with 500 mg of each drug at a similar interval (7).

In addition to systemic therapy, sebaceous adenitis can benefit from a variety of topical treatments aimed at alleviating clinical signs and improving skin and coat health. Topical therapies play an essential role, particularly in mild cases or as part of a comprehensive treatment plan, and include shampoos, humectants and oil soaks. Specialized shampoos containing sulfur and salicylic acid are an integral part of managing sebaceous adenitis, typically used 2-3 times a week, with a 10-minute contact time before rinsing (1,18). During bathing, a soft brush can be employed to assist in the removal of scaling. After rinsing, a conditioner can be applied, or a 50-75% dilution of propylene glycol can be sprayed or rinsed onto the dog's coat (9,18). These sprays are sometimes used daily and then reduced to 2 to 3 times per week for ongoing maintenance. Propylene glycol acts as a humectant, helping to retain moisture (9,18). Additionally, baby oil soaks, where neat oil or a 1:1 dilution with water is massaged into the coat and left for 1-6 hours, can also be used. Following this, the dog should be bathed using shampoo or dishwashing liquid to remove excess oil (9).

Prognosis

The prognosis for dogs with sebaceous adenitis can vary depending on several factors, including the severity of the condition, the response to treatment, and the overall health of the individual animal. For mild cases, where the clinical signs are relatively limited and responsive to treatment,

the prognosis is generally more favorable. With appropriate management, affected dogs can frequently enjoy a comfortable quality of life, with noticeable improvement in their skin and coat health. However, in more severe and advanced cases of sebaceous adenitis, the prognosis may be guarded. While treatment options are available to alleviate clinical signs and improve the quality of life, it is important to recognize that sebaceous adenitis is typically a chronic condition. Long-term management is often required, and relapses can occur even during treatment (6,8). It is, therefore, crucial for owners and veterinarians to work together to develop a tailored treatment plan for each case. Regular follow-up appointments and adjustments to the treatment regimen are common to ensure the best possible prognosis, and despite the chronic nature of the condition, with diligent care and appropriate therapy many dogs can enjoy a good quality of life.

CONCLUSION

Canine sebaceous adenitis is a complex dermatological disorder with diverse clinical manifestations. Its multifactorial etiology involves genetic predisposition, immune system dysfunction, and environmental factors. Diagnosis requires a comprehensive approach, and treatment options range from systemic immunosuppressive drugs to topical therapies. The prognosis varies, with long-term management often necessary, and a tailored treatment plan is crucial for each affected dog to optimize their quality of life.

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CANINE PRURITUS: CAUSES AND THERAPIES

Understanding what causes an animal to itch is the first step in successful treatment of the pruritic dog, as this article describes.

KEY POINTS

1. The approach to treating pruritus should first follow a systematic process that makes it possible to confirm or rule out the principal causes.
2. The pathophysiology of pruritus varies depending on the pathology presented by the animal; mediators of pruritus differ and may partly explain the lack of response to certain antipruritics.
3. There are several therapeutic strategies that can be applied to control pruritus, but none of them are effective in all cases.
4. The best antipruritic is the one that treats the etiology of the condition, if a cure is possible, or the one that causes the least side effects.

Introduction – what is pruritus?

Pruritus or itching is defined as "an unpleasant sensation provoking a reflex, which in animals can take the form of scratching, biting or sucking, rubbing against surfaces or excessive licking" (1,2). Sometimes the signs of pruritus can be subtle and simply cause hair loss (self-inflicted alopecia), but it can also lead to skin lesions (3). This behavior is the animal's way of protecting itself against external irritants (such as insects, chemical agents or poisonous plants (1,2,4)), but it can negatively affect the pet's quality of life and that of its owners if the condition is chronic (5).

Pruritus is one of the main complaints encountered in small animal dermatology (2). In human medicine, it is classified according to its type (acute, chronic, neuropathic, pruriceptive or psychogenic) or its clinical presentation (dermatological, systemic, neurological, psychogenic, mixed or other) (1,6,7). There is no clear categorization of pruritus for animals, although dermatological **(Figure 1)**, psychogenic **(Figure 2)** and neuropathic **(Figure 3)** etiologies have been described (2,3). More commonly associated with a dermatological etiology, the exact sensation experienced by the animal cannot be precisely defined (3). Indeed, there are various sensations, which are better described in humans, such as burning, tingling, stinging or numbness (1), that could cause an animal to scratch or bite (3).

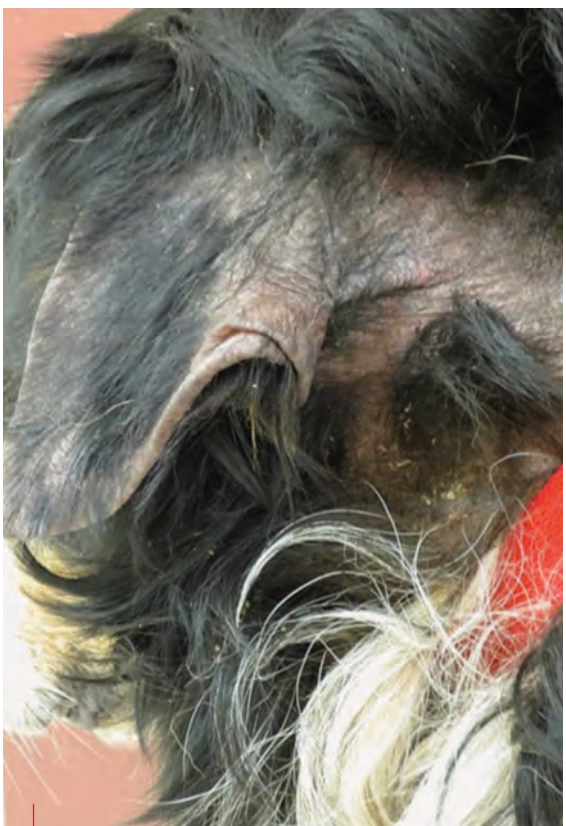

Figure 1. Self-inflicted alopecia localized on and around the pinnae in a dog presenting with sarcoptic mange (dermatological disorder).

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The signs of pruritus are the physiological result of a motor response caused by stimulation of the thalamus. Activation of the thalamus varies depending on the neurons that are stimulated, which may be either histaminergic or non-histaminergic (1,2,8). Although there are several mediators involved in pruritus, there are two predominant neurophysiological pathways routing the pruritus signal from the skin to the thalamus. The first is a histamine-stimulated pathway involving primary afferents that are unresponsive to mechanical stimuli, and the second is a histamine-independent pathway induced by the activation of cutaneous nociceptors (1,2,9). Pruriceptors will be present in the skin, but it is not clear if these receptors would truly be distinct from nociceptors (9,10).

When an irritating substance causes a sudden (acute) cutaneous reaction, the pruriceptors are activated, causing local cells to release a myriad of pruritogenic substances. The skin cells most effective in releasing these substances (histamine, cytokines, proteases and chemokines) are keratinocytes, mast cells and basophils. The key molecule in relation to acute pruritus is histamine, binding to H1 and H4 receptors on free histaminergic nerve endings (2,7,8). If the pruritus and inflammation resulting from a trigger is successful in suppressing the aggressor, then the pruritus should not persist more than a few days (7).

However, chronic pruritus, unlike acute pruritus, is usually induced by non-histaminergic chemical or mechanical stimuli, caused by a systemic condition or skin disease. It involves a series of complex events leading to a constant release of pruritogenic mediators (1,4). Chronic exposure to pruritogenic substances can potentially lead to peripheral or even central sensitization (1,8). This phenomenon of sensitization, defined as increased sensitivity to low-pruritic or non-pruritic stimuli (1), has not been well-described in relation to either canine or feline species. Nevertheless, peripheral or central sensitization could be significant following chronic exposure to inflammatory mediators, as it could modify the pruritus threshold, particularly with respect to allergies. At the peripheral level, this threshold may be altered by various mechanisms, such as an intraepidermal increase in pruriceptors or an increase in the number of mast cells (1,8-11). At the central level, sustained pruritus could modify the transmission of the pruritus signal along the spinal cord and the spinothalamic pathway and alter the functions and structure of the brain (8,10,11).

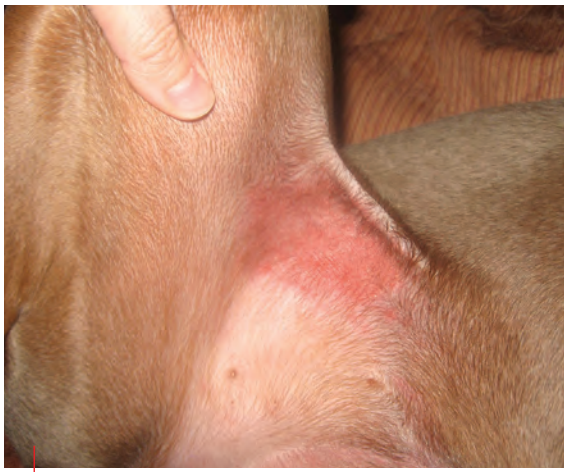

Figure 2. Note the rash around the groin and left side of this Doberman Pinscher following repeated sucking of the area (psychogenic disorder).

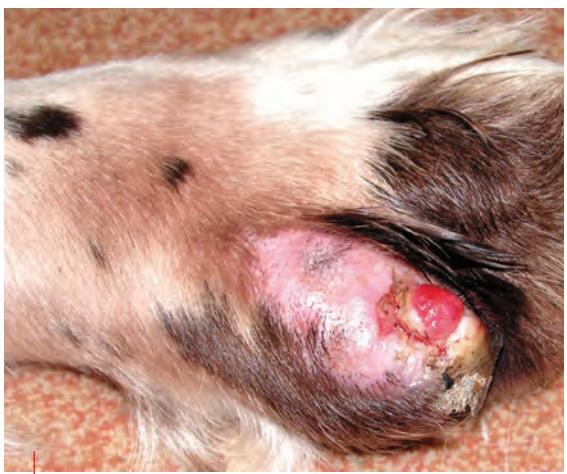

Figure 3. Acral mutilation syndrome in a French Spaniel. The matrix of the claw is exposed and there is an extensive area of alopecia on the dorsal surface of the toe. These wounds are self-inflicted (neuropathic disorder).

This brief review of the pathophysiology of pruritus may help understand why many animals do not respond to antihistamines in cases of chronic pruritus caused by, say, an allergy, or why the concurrent administration of several antipruritics is sometimes required.

DERMATOLOGICAL HISTORY

Date .....

Main complaint: .....

Age at purchase: ..... **Source:** ❑ **Animal shelter** ❑ **Pet shop** ❑ **Private owner/breeder**

- At what age did the problem begin? .....
- Where did the problem begin? .....
- Appearance at the beginning: .....
- Evolution of dermatosis: .....
- Are there any other pets in the house? .....
- If so, species: .....
- Are there any other pets affected? or humans? If so, describe the skin lesions: .....
- Does the pet receive preventive flea treatment? If so, which one and for which period(s) of the year? .....
- Describe the pet's indoor environment (where the pet sleeps, type of flooring, if there is mold, etc.): .....
- Describe the animal's external environment (urban vs. rural, swimming, etc.): .....
- % of time indoors: .....
  % of time outdoors: .....
- Does the pet have signs of pruritus (scratching, biting, licking, rubbing)? .....
- Intensity of pruritus on a scale of 0 to 10 (0= none, 10 = continuously/nocturnal pruritus): .....
- Pruritus areas: Year-round or seasonal ?
  If seasonal, is it worse?
  ❑ in spring ❑ in summer
  ❑ in fall ❑ in winter
- Does the pet have runny eyes and/or nose? .....
- Or does the pet sneeze? .....
- Complete history of diets offered: .....
- Does the pet have digestive problems (flatulence, diarrhea, belching, vomiting, etc.)? .....
- What drugs are used (doses, dates of administration) and what effects are obtained?
- Is the pet currently on medication? .....
- Other diseases?
- Other important facts (travel, grooming, boarding, baths, dog park, etc.)?

Figure 4. An example of a dermatological questionnaire.

Overall approach to pruritus

When presented with a case of pruritus, the first step should be to compile a complete case history, which can include a standard dermatology-related questionnaire **(Figure 4)** and information concerning other systems (for example, if a dog is excessively licking one of its limbs, this could be an indication of pain secondary to (say) osteoarthritis, rather than pruritus). The use of a visual analogue scale[1] **(Figure 5)**, whereby the owner assesses the degree of pruritus by marking on a line how severe they perceive the itch to be, can be very helpful for both the initial exam and for follow-ups. Background information, such as the age at which clinical signs first appeared and the breed, can sometimes help aid the diagnosis. For example, lateral phantom scratching around the cervical region in a Cavalier King Charles Spaniel is highly suggestive of primary secretory otitis media, which is often associated with syringomyelia (12). Similarly, flank sucking in a young Doberman Pinscher may suggest a behavioral disorder (3,13).

The second step should be to identify any skin lesions and how they are distributed. For example, lumbosacral lesions could suggest flea allergy dermatitis, while pruritus around the ventral region and face might indicate atopic dermatitis **(Figure 6)** (14).

Once the examination is complete, the most common causes should be ruled out; these include skin infections (bacterial and fungal), ectoparasites, and skin hypersensitivities associated with food or environmental allergens (14,15). This requires a rigorous approach, following a series of logical steps, which makes it possible to confirm or rule out a skin infection or parasitic infestation before then addressing food and environmental allergies. If pustules, collarettes or crusted, eroded or ulcerated lesions are present, a simple cytological examination **(Figure 7)** of the lesions will be essential. This will make it possible to identify a bacterial (*e.g.*, *Staphylococcus*) or fungal (*e.g.*, *Malassezia, Candida*) infection or overgrowth that may either cause the pruritus or at least be a contributing factor (2,14,15). Where erythema is present, regardless of whether it is associated with papules, areas of alopecia, comedones, or crusty or scaly lesions, a search for ectoparasites using skin scrapings, a flea comb, a tape-test or an oil smear (for the ears) is recommended (2,14,15). Sometimes a search will be unsuccessful, and the only way to confirm or rule out this hypothetical diagnosis will be a trial course of treatment with a broad-spectrum antiparasitic (14).

Other potentially useful diagnostic tests include a ultraviolet (Wood's) lamp, a fungal culture test, or a polymerase chain reaction (PCR) test for dermatophytes, bacterial culture, and skin biopsies (2,15). However, skin biopsies are rarely useful for the etiological diagnosis of a pruritic skin condition. These should be reserved for atypical clinical cases or cases where the animal does not respond to antimicrobial or antiparasitic treatments and it is not possible to demonstrate skin hypersensitivity.

[1] https://www.cavd.ca/images/CAVD_ITCH_SCALE.pdf

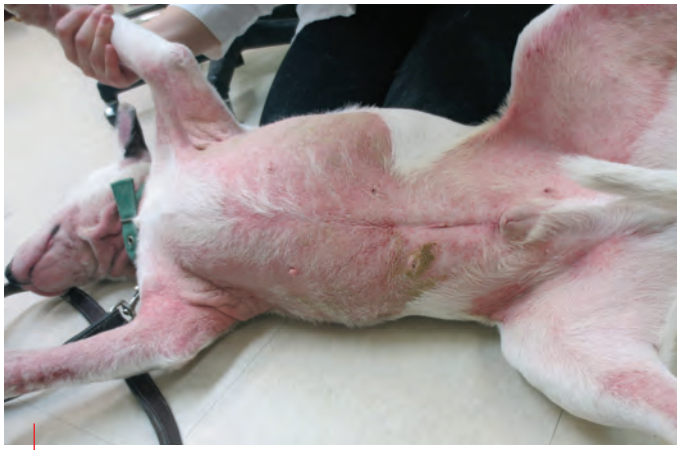

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Figure 6. Atopic dermatitis in a Bull Terrier. Generalized erythema with a ventral appearance, including the muzzle and chin. Note the lichenification in the armpits and abdominal region, associated in some places with yellowish crusts, reflecting the chronicity of the dermatitis. These sites are classically targeted by atopic dermatitis in dogs.

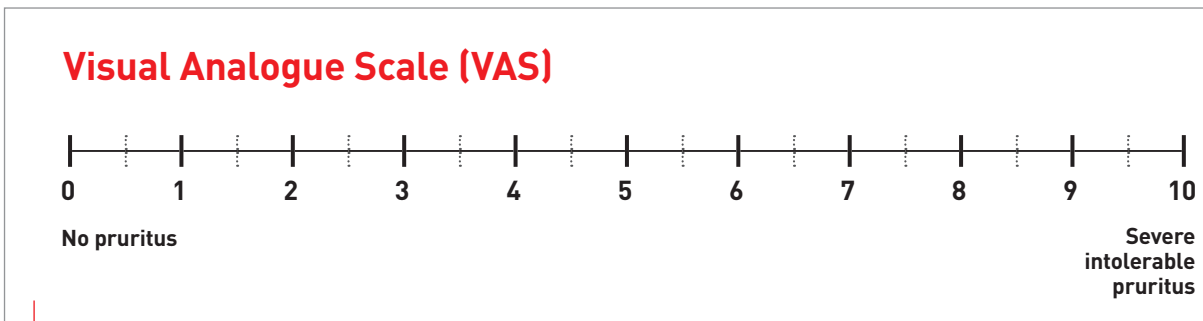

Figure 5. The visual analogue scale is designed to measure the severity of itching. An owner can place a mark anywhere on the line to indicate the point at which they think their pet's level of itchiness currently lies. So for example, 2 = very mild itching, 6 = regular episodes of moderate itching, 10 = extremely severe/almost continuous itching.

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Figure 7. Different sampling techniques for cytological examination (**(a)** swab; **(b)** impression smear; **(c)** adhesive tape). The chosen technique should take into consideration the type of lesion (crusts, ulcers, fistulas, etc.) in order to obtain maximum cytological findings.

Biopsies are recommended for skin conditions that are suspected to be caused by an autoimmune condition (such as pemphigus foliaceus) **(Figure 8)** or a tumor (such as cutaneous epitheliotropic lymphoma) (2,15).

Once any skin infections and infestations have cleared, any potential hypersensitivity can be investigated by way of an 8-week elimination diet. This should consist of a veterinary diet containing a source of hydrolyzed protein (ideally a novel one for the animal). Alternatively, a diet containing a new source of protein for the individual animal can be used, but bear in mind that many cross-reactions have been demonstrated between different sources of animal protein. An allergy test (whether intradermal or serological) should be the last step in the investigation process if pruritus persists despite an elimination diet. It should be noted that the diagnosis of atopic dermatitis relies on background information, the case history and a clinical picture compatible with hypersensitivity in the absence of infection, infestation or adverse food reactions. Allergy testing only serves to identify potential environmental allergens in order to then begin allergen immunotherapy (14,15).

Managing pruritus: general concepts

The main causes of pruritus can be grouped into four major categories: parasites, inflammatory skin conditions (infectious, irritants and autoimmune or immune-mediated conditions), allergies and neuropathies/neoplasms (2,15). These categories are not mutually exclusive, and it is possible for pruritus to be caused by two separate conditions simultaneously. The best way of controlling pruritus is to remove the causative agent from the environment. Identifying and removing an irritant (contact with a poisonous plant or chemical; a foreign body; recent use of shampoo, sunscreen, insecticide spray or powder; flea collar; etc.) may cure the condition. Similarly, antimicrobials and antiparasitics will be the best antipruritic treatments if there is a skin infection and/or ectoparasites are present. In the case of skin

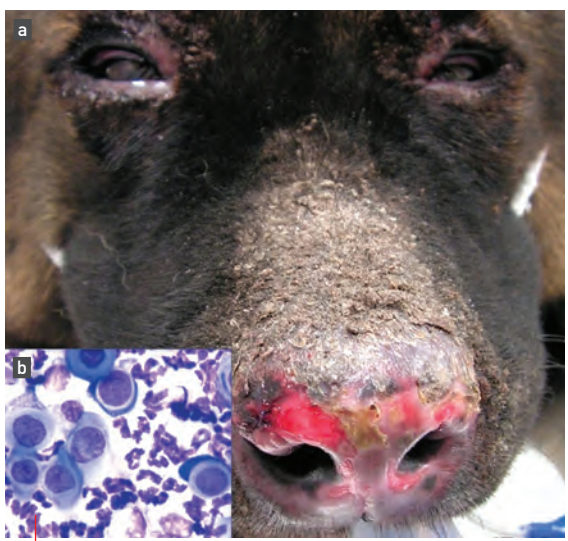

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Figure 8. **(a)** The distribution of crusty lesions in this Akita is typical of pemphigus foliaceus. Note the involvement of the nose, which shows depigmentation, erosions, and ulcers, as well as crusts on its dorsal aspect. Although the identification of acantholytic keratinocytes accompanied by neutrophils **(b)** on subcrustal cytological examination is suggestive of pemphigus foliaceus, it is the histopathological examination that will establish the definitive diagnosis.

Table 1. Reported side effects following systemic and topical administration of glucocorticoids.

System	Side effects
Integumentary system	• Skin atrophy • Alopecia • Comedones • Prominent dermal blood vessels • Phlebectasia • Purpura • Subepidermal blisters • Hypopigmentation • Delayed wound healing • Bacterial pyoderma • Demodectic mange • Calcinosis cutis • Squamosis
Cardiovascular/ metabolic system	• Hypertension • Panting • Hyperlipidemia • Glucose intolerance hepatomegaly • Redistribution of fats, obesity • Polyphagia • Polyuria, polydipsia
Endocrine system	• Infertility, anestrus, testicular atrophy • Miscarriage • Delayed growth • Adrenal atrophy • Iatrogenic hyperadrenocorticism • Alteration in thyroid hormones
Gastrointestinal system	• Gastrointestinal ulcers • Gastric bleeding • Intestinal perforation
Musculoskeletal system	• Osteoporosis • Atrophy, muscular weakness • Abdominal distension • Exercise intolerance • Ligamentous laxity
Others	• Immunosuppression • Behavioral changes (irritability, aggression, lethargy) • Glaucoma, cataracts • Peripheral neuropathy

allergies, including flea bite allergies, atopic dermatitis and adverse food reactions, avoiding the allergen, if possible, will cure the condition (16). Aggressive flea management in the case of flea allergy dermatitis, and diet control in the case of adverse food reactions, will help control pruritus, but where environmental allergens are involved avoidance is rarely possible. Here, other long-term strategies should be implemented, including allergen immunotherapy, steroidal or non-steroidal antipruritics, and biological therapies (16). Potential causes of skin allergies include drug hypersensitivity and allergic contact dermatitis, and in these cases withdrawal of the drug or removal of the substance or object responsible should put an end to the pruritus. Finally, in suspected cases of

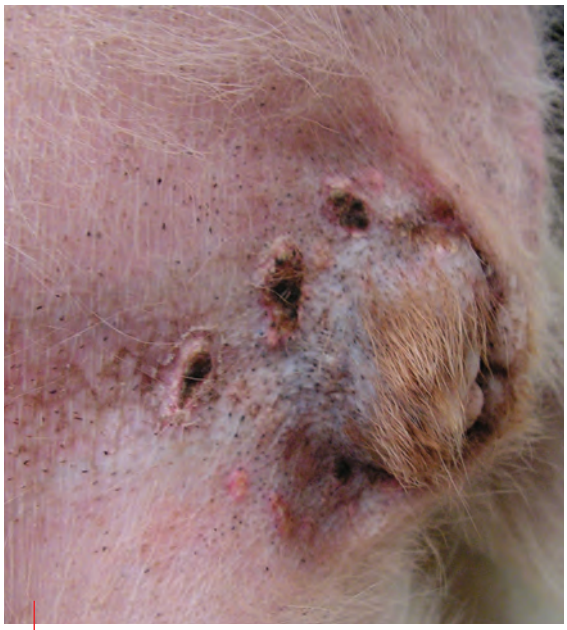

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Figure 9. Cutaneous side effects following prolonged oral administration of glucocorticoids to a dog suffering from atopic dermatitis. Note the presence of calcinosis cutis and comedones around the pudendum, and also wrinkling of the skin on the abdomen, suggesting thin hypotonic skin.

psychogenic or neurogenic conditions, preferred treatments include behavioral therapies (such as tricyclic antidepressants or selective serotonin reuptake inhibitors (2,8)), or treatments targeting peripheral or central neurological pathways (such as gabapentin or pregabalin) (2,8,9).

Antipruritic treatments

Acute pruritus

Antipruritic drugs can be useful in the short term to quickly ease the discomfort for the animal while an attempt is made to identify and control the causal agent. Here the most effective treatments will often be topical or systemic glucocorticoids (at an anti-inflammatory dose) due to their powerful anti-inflammatory effect and the fact that they are fast-acting. Since they act on various aspects of the inflammatory cascade and pruritus pathways, they are particularly effective in cases of pruritic inflammatory dermatosis if used diligently (2,16-18). However, glucocorticoids (both topical and systemic) have many side effects **(Table 1)**, particularly when used over a prolonged period of time **(Figure 9)**.

Chronic pruritus

There is no single solution that can effectively control all types of pruritus. The majority of studies published researching antipruritic treatments have focused on allergic dermatitis, and have looked at various therapeutic targets. Cytokines with the potential to induce pruritus in canine atopic

dermatitis include interleukins (IL)-4, IL-13, IL-31 and IL-33, and thymic stromal lymphopoietin (TSLP) (1,7,16,19). The latter is linked to a type-2 immunological response (type 2 T helper lymphocytes) (whereas in cats, which have been studied less, histamine, IL-4 and IL-31 are potential candidates as mediators of pruritus (16,20)).

In chronic pruritus caused by an allergy, while topical treatments such as glucocorticoids and tacrolimus 0.1% can be effective, their application is often limited by the animal's fur, the size of the areas to be treated, and (although more often in cats) the grooming behavior (2,18,21). In cases of chronic and generalized pruritus, systemic treatments are preferred. The most commonly used systemic antipruritic treatments are glucocorticoids, oclacitinib, cyclosporine and lokivetmab **(Table 2)**.

Glucocorticoids

The most commonly prescribed oral glucocorticoids remain prednisone and methylprednisolone. This class of drug is an affordable and effective way of addressing acute episodes of pruritus and controlling chronic dermatosis, as long as the dose and the frequency of administration are low (2,17,19). Long-acting injectables should be avoided due to their side effects.

Oclacitinib

Oclacitinib is a treatment of choice for both acute and chronic pruritus in dogs over 12 months old due to its fast onset (peak plasma is reached in just one hour). Its inhibitory action on the JAK-STAT pathway interferes with the activity of important pruritogenic cytokines, including IL-4, IL-13 and particularly IL-31 (21).

Table 2. Systemic antipruritic treatments to manage canine pruritus, particularly for cutaneous hypersensitivity.

Treatment	Dosage
Predniso(lo)ne/ Methylpredni-solone	0.5 mg/kg administered orally q24h until pruritus under control; the frequency of dosing and then the size of the dose should be gradually reduced until the ideal dose/ frequency to maintain comfort is found.
Oclacitinib	0.4-0.6 mg/kg administered orally q12h for 14 days, then q24h. It is possible to begin with q24h for mild to moderate cases of pruritus.
Cyclosporine	5 mg/kg administered orally q24h for 4 to 6 weeks. The dose and/or frequency of administration can be then occasionally reduced. The administration of frozen capsules or a chilled oral solution helps reduce gastrointestinal side effects.
Lokivetmab	1-2 mg/kg administered via subcutaneous injection q4 week or as needed.

Cyclosporine

Cyclosporine inhibits calcineurin in CD4+ T lymphocytes, which alters the release of potentially inflammatory or pruritogenic cytokines. Oral cyclosporine is indicated for controlling allergic dermatitis as it affects different aspects of the immune response (reducing the synthesis of IL-2 and IL-4, altering the number of mast cells and their histamine content, altering the survival and function of eosinophils, and reducing serum IL-31) (22,23). However, it needs to be administered for a minimum of 4 weeks in order to notice any decrease in pruritus in dogs, and, therefore, is more useful in treating chronic conditions (2,17).

Lokivetmab

A biological therapy intended for dogs only, lokivetmab is a "caninized" monoclonal antibody that targets circulating IL-31. Highly effective in controlling pruritus, particularly in relation to atopic dermatitis, this treatment stems from a major discovery: the critical role that IL-31 plays as a mediator of pruritus in canine atopic dermatitis (21,24). It is very safe and there are no known interactions with other drugs or associated diseases. This treatment is indicated for acute or chronic pruritus (as it starts to act in less than 3 days) (21).

"Skin biopsies are rarely useful for the etiological diagnosis of a pruritic skin condition; they should be reserved for atypical clinical cases or where the animal does not respond to antimicrobial or antiparasitic treatments and it is not possible to demonstrate skin hypersensitivity."

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Antihistamines

For the reasons mentioned above, the beneficial effects of antihistamines are modest. At best, they can be used to treat cases of mild pruritus, as an occasional or regular treatment once an episode of acute pruritus is under control (2,17). Furthermore, it is often necessary to try various antihistamines in order to find the right one for an individual animal.

Others

Amitriptyline is a tricyclic antidepressant with antihistamine properties; tests show it to at least partially control pruritus in about 32% of dogs (25). Other treatments have also been studied (such as misoprostol, arofylline, pentoxifylline and azathioprine), but the results do not suggest that they are particularly effective in managing pruritus (2).

CONCLUSION

The key to success is a systematic approach that allows the different causes of pruritus to be eliminated one by one. Maintaining good communication with the owner and using clinical tools such as diagrams, algorithms or information sheets will help ensure that the owner is engaged in the process and understands the steps to follow. Regular pruritus intensity examinations and assessments should be used in order to ensure the most appropriate diagnosis and treatment. Chronic pruritic dermatoses can seriously affect the psychological and physical health of both animals and their owners, and a better understanding of the pathogenesis of the animal's condition and the mediators of pruritus will help ensure more effective use of the various treatments available. This way the owner can be reassured that their pet will eventually enjoy greater comfort and well-being.

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CANINE PYODERMA: A TIERED APPROACH

Our knowledge regarding canine pyoderma continues to evolve; this paper describes current thinking as to how we should approach such cases.

KEY POINTS

1. Pyoderma is a bacterial infection of the skin presenting acutely as papules, pustules, crusts and epidermal collarettes; or chronically as alopecia, hyperpigmentation and ulceration.
2. Methicillin-resistant *Staphylococcus pseudintermedius* prevalence has significantly increased over the last 10 years and necessitates antimicrobial stewardship guidelines going forward.
3. Topical therapy, which is equivalent to systemic therapy, is the preferred treatment for superficial pyoderma in order to decrease the amount of systemic antimicrobial exposure.
4. Systemic therapy for pyoderma should abide by the tier system, with Tier 1 being used as empirical therapy and Tier 2 only used when a culture indicates susceptibility.

Introduction

Pyoderma is a bacterial infection of the skin, generally divided into superficial and deep categories depending on the layer of the skin that is affected. Clinical lesions of superficial pyoderma include erythematous papules and pustules **(Figure 1)** which may be centered on hair follicles. Honey-to-brown colored crusts **(Figure 2)** are also often present on the skin and may be adhered to the hair shafts. Epidermal collarettes **(Figure 3)**, which develop as an annular area of scale, may be noted as well. In more chronic cases, alopecia, hyperpigmentation and ulcerations are to be found **(Figure 4)**. Deep pyoderma lesions are noted clinically by ulcers and draining tracts **(Figure 5)** (1).

Causative organisms

The bacteria associated with a pyoderma are basically an overgrowth of the animal's normal flora; the most common bacteria identified in pyoderma are coagulase positive *Staphylococcus* species. Of these, *S. pseudintermedius* is the most common in dogs, whilst *S. aureus*, another coagulase positive organism, has also been identified as an offending bacteria, but is more prevalent in cats. *S. schleiferi* has been reported as the second most common bacteria in canine pyoderma, and a unique aspect of this organism is that it is a coagulase variable species; some reports identify it as coagulase positive, while others note it as coagulase negative (2). Historically, coagulase negative *Staphylococcus* spp. have been identified as being non-pathogenic, but newer reports are showing these bacteria (which include *S. epidermidis, S. xylosus*, and *S. haemolyticus* (1,3,4)) can be pathogenic. Occasionally, *Streptococcus canis*, *Pseudomonas aeruginosa*, *Corynebacterium auriscanis*, *Escherichia coli* and *Proteus* spp. are identified as the causative bacteria in a pyoderma (1).

Antimicrobial resistance

Bacteria are constantly evolving and acquiring resistant mechanisms or genetic mutations, and *Staphylococcus* spp. are well-known for

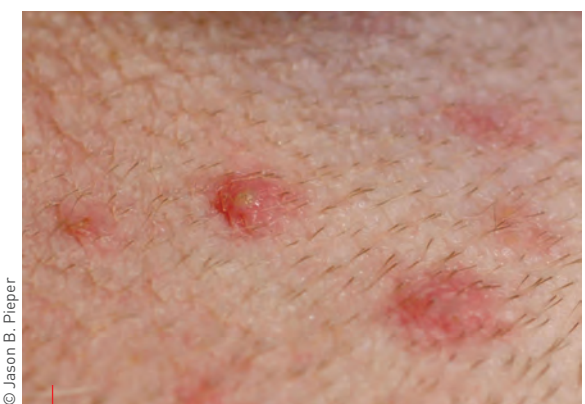

Figure 1. A pustule is present in the center of the image, with a papule in the bottom right.

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some of their genetic mutations to circumvent antimicrobials. A common one identified in 80-94% of *S. pseudintermedius* cases is the *blaZ* gene mutation, which is known for resistance to beta-lactams, hence amoxicillin, ampicillin, and penicillin are not effective. Amoxicillin still may be effective in these cases if it is potentiated, *e.g.*, with amoxicillin-clavulanic acid (5,6).

A bigger concern in veterinary medicine from a One Health perspective is the *mecA* gene mutation. This encodes for an altered penicillin-binding protein (PBP2a) with low affinity to all ß-lactams, including penicillins, cephalosporins, and carbapenems, meaning that ß-lactams cannot bind to the bacterial cell wall to kill the organism. This genetic mutation is referred to as methicillin-resistant *staphylococcus* (MRS), with the species noted afterwards; for example methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) and methicillin-resistant *Staphylococcus aureus* (MRSA) (2,7). A new generation of cephalosporins has been developed that are effective against MRSA, but these should be reserved for human medicine. It is common for MRS to express resistance to a combination of other drugs, including aminoglycosides, chloramphenicol, fluoroquinolones, lincosamide, tetracyclines, potentiated sulfonamides and rifampicin. These cases may then be considered multidrug-resistant (MDR) if they are resistant to two additional antimicrobial classes, or extensively drug-resistant (XDR) when they are resistant to all but two or fewer antimicrobial classes (2,7).

Prevalence and risk factors

MRSP was first identified in animals in 2005 in Belgium (8), and since then it has been identified in animals in most, if not all, countries. Its prevalence, however, shows considerable geographical variability, which may be due to different antimicrobial stewardship guidelines and antimicrobial restrictions. In 2011, rates of MRSP were reported from 0-4.5% in dogs in the community and up to 7% of dogs with skin disease. At that time, anywhere from 30-66% of *S. pseudintermedius* isolates were methicillin-resistant, depending on the country (9). A recent study in the United States showed that the prevalence of *S. pseudintermedius* isolates resistant to oxacillin (determinant for methicillin resistance) has statistically significantly increased between 2010 and 2021 (10), whilst another US study showed an increase of MRSP from 28% in 2010 to 80% in 2020 (11). The prevalence has seen a significant increase in the last 10 years worldwide.

In terms of risk factors, one study noted dogs with a history of being treated with antimicrobials within the last month have an increased risk of MRSP compared to methicillin-susceptible *Staphylococcus pseudintermedius* (MSSP) (5). Another study showed animals given antibiotics in the previous year had an increased risk of being multidrug-resistant (11). Development of MRSP has also been linked with previous fluoroquinolone exposure (12).

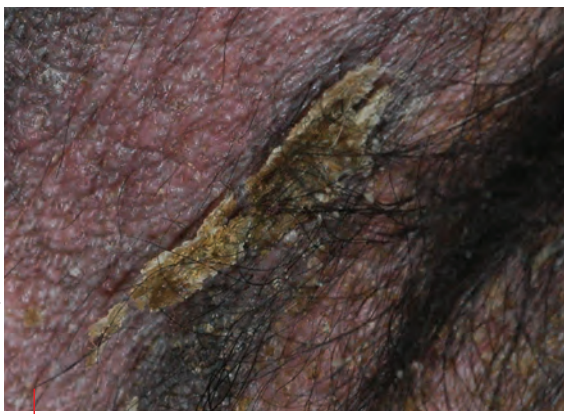

Figure 2. A large crust with embedded hair typical of superficial pyoderma.

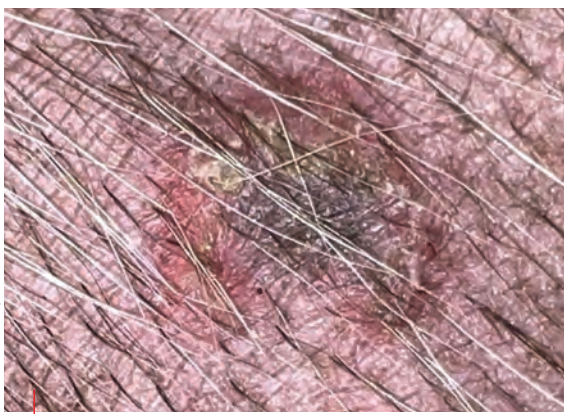

Figure 3. An epidermal collarette, with the periphery showing erythema and scale, while the center is hyperpigmented.

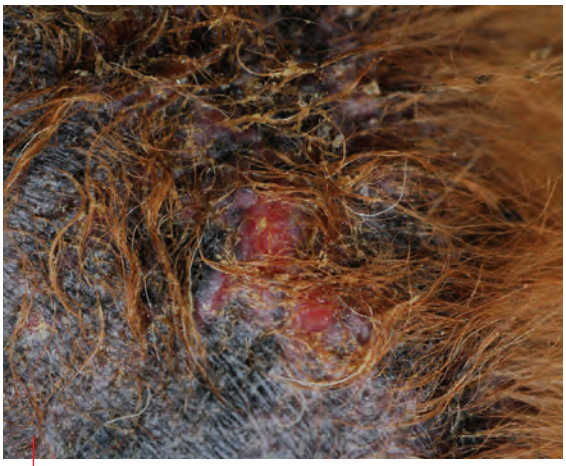

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Figure 4. A case of chronic superficial pyoderma, with a moderate amount of hyperpigmentation on the left of the image and some crusts present in the hair. Additionally, multifocal ulcerations are present.

Diagnosis

Cytology

The easiest and most efficient way for a diagnosis of pyoderma is cytology of clinical lesions (pustules, crusts, epidermal collarettes). There are a variety of ways to do this, including direct impression, tape cytology, cotton-tipped applicator, and the slurry technique (13). The type of sampling method is based on the characteristics of the lesion to be sampled. For example, pustules and ulcerations are easily sampled with direct impression since exudate is present. Tape cytology may be a better option for crusts and epidermal collarettes due to their dry nature. Observance of inflammatory cells with associated bacteria **(Figure 6)** is supportive of a pyoderma, and when the inflammatory cells contain intracellular cocci **(Figure 7)**, diagnosis is confirmed (1).

Bacterial culture

When there is a lack of response to empirical antimicrobial therapy, bacterial culture and susceptibility are necessary to determine the appropriate systemic antimicrobial. It is never wrong to culture a pyoderma, but there are criteria when it is highly recommended. Current recommendations for bacterial culture and susceptibility include the following:

1. less than 50% reduction of lesions within two weeks of appropriate systemic antimicrobial therapy;
2. emergence of new clinical lesions (papules, pustules, epidermal collarettes, crusts) two or more weeks after appropriate antimicrobial therapy with a cytological diagnosis of pyoderma;
3. presence of clinical lesions after six weeks of antimicrobial therapy alongside a diagnosis of pyoderma based on cytology;
4. intracellular rod-shaped bacteria identified on cytology;
5. a prior history of multidrug-resistant infection in the animal or a household animal (1).

Pustules are the ideal lesion to sample, as they can be lanced and sampled with the culturette swab. Sampling with the culturette swab under crusts is also a good option if there is purulent exudate present. If the lesion is completely dry, such as a crust or an epidermal collarette, an ideal method to use is saturating the culturette swab with saline prior to rubbing the skin. This method has been shown to obtain a higher number of bacteria compared to a dry swab (14). None of the above sampling methods requires any surface disinfection. However, if planning to biopsy the skin for tissue culture, it is recommended to clean the surface to remove contaminants (1).

Treatment

Treatment of a superficial pyoderma can be accomplished with either topical or systemic therapy, or a combination of both. With the increase in antimicrobial resistance, there has been a push to use more topicals in place of systemic antimicrobials (10). One study demonstrated no difference when canine superficial pyoderma was treated with a systemic antimicrobial (amoxicillin-clavulanic acid) or a topical chlorhexidine shampoo and solution over a 4-week period (15).

Topical therapy

Topical therapy has historically been underutilized for treating superficial pyoderma (1), but it has the benefit of achieving a higher concentration of drug compared to what can be delivered systemically. Additionally, since the therapy is applied directly to the skin, drug concentration is not decreased via metabolism. When deciding to use topical therapy, two decisions are necessary; i) what active ingredient to use, and ii) which formulation would be ideal for the situation.

In terms of active ingredients, chlorhexidine is widely accessible, and the most common agent used. It is available in a variety of concentrations (2-4%) and some products

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Figure 5. Deep pyoderma showing an ulcerated area with serosanguinous discharge.

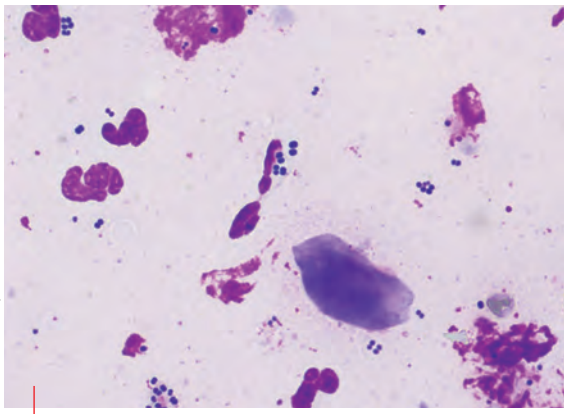

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Figure 6. There are quite a few extracellular pairs or clusters of cocci present on this microscopic sample, raising suspicion of a pyoderma (1000x magnification).

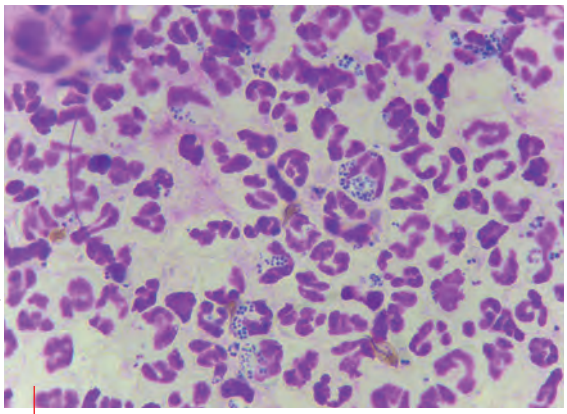

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Figure 7. A large number of intracellular pairs or clusters of cocci are present within neutrophils in this image, which would confirm a diagnosis of pyoderma (1000x magnification).

will combine it with an antifungal, such as miconazole, ketoconazole or climbazole. There are studies available showing the concentration of chlorhexidine does not directly correlate to efficacy; for example, a 4% chlorhexidine shampoo is not superior to a 2% chlorhexidine/2% miconazole shampoo. Chlorhexidine has been shown to be equally successful in treating MRSP and MSSP, and while resistance to chlorhexidine is a common concern, there is no evidence to suggest that this is a clinically relevant problem (16).

Benzoyl peroxide and ethyl lactate are the next most common active ingredients after chlorhexidine. Benzoyl peroxide has been shown to be effective in treating superficial pyoderma, but the formulations available are significantly limited. Some reports have shown variable results regarding its success, but it should be noted that *in-vivo* studies are necessary to show the true activity of benzoyl peroxide – the reason being that the interaction with the skin will produce highly reactive oxygen radicals, which are very potent against bacteria. Ethyl lactate is similar to benzoyl peroxide in multiple aspects, but again formulations are limited and again *in-vivo* studies are necessary to show the true activity of this ingredient, because of the necessary skin interaction that hydrolyzes it into ethanol and lactic acid (16).

Some of the newer active ingredients that have shown success in treating superficial pyoderma include sodium hypochlorite, accelerated hydrogen peroxide, silver compounds, and essential oils or plant extracts. Diluted bleach, which has the active ingredient of sodium hypochlorite, has previously been shown to be effective against *S. pseudintermedius* (16), and it also appears to be tolerated on the skin when diluted down to 0.005% in healthy dogs (17). Sodium hypochlorite is available in combination with salicylic acid in a shampoo formulation in some countries. Accelerated hydrogen peroxide has also been shown to be effective and comes in a shampoo. Silver compounds are an attractive active ingredient when used in combination with other products such as chlorhexidine, with several formulations available.

Some essential oils and plant extracts have been added to topical products to aid in the resolution of pyoderma or help in prevention (16).

The variety of formulations available for topical therapy include shampoos, sprays, wipes, mousses, rinses, conditioners, gels, creams and ointments. One way to decide which formulation may be preferred is the extent of the disease, whether generalized, localized or focal. For generalized disease; shampoos, sprays, mousses, rinses, and conditioners would be ideal. For localized or focal lesions; wipes, gels, creams and ointments are good options. Shampoos are by far the most common formulation available with the widest variety of active ingredients. Typical regimen for shampoos, sprays and mousses include 2-3 times weekly until 7 days past resolution, with shampoos allowed a contact time of 10 minutes prior to rinsing. Wipes, gels, creams, and ointments should be used daily (1).

"Diet can also be beneficial to prevent pyoderma and lessen recurrence and severity of clinical signs from atopic dermatitis; one study in affected dogs fed an appropriate diet showed a decrease in signs of atopic dermatitis over a 9-month period."

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Table 1. Systemic antimicrobial tiers.

Tier	Antimicrobial
1st Tier Primary choice for empirical therapy for pyoderma	• Clindamycin or lincomycin • First-generation cephalosporin (*e.g.*, cephalexin, cefadroxil) • Amoxicillin-clavulanate • Trimethoprim- or ormetoprim-potentiated sulphonamides
1st or 2nd Tier	• Third-generation cephalosporins (cefpodoxime, cefovecin)
2nd Tier Used when empirical therapy and topical therapy are not appropriate, and culture indicates susceptibility	• First-tier antimicrobials (clindamycin, potentiated sulphonamides, cephalosporins) when culture indicates susceptibility • Doxycycline or minocycline • Chloramphenicol • Fluoroquinolones (enrofloxacin, marbofloxacin, orbifloxacin, pradofloxacin, ciprofloxacin) • Rifampicin • Aminoglycosides (amikacin, gentamicin)
3rd Tier When 1st and 2nd Tier (as well as topical therapy) are not appropriate, and culture indicates susceptibility	• Linezolid • Teicoplanin • Vancomycin

Finally, fluorescent light energy is a newer technology that has been used recently for both deep and superficial pyoderma. This technology combines fluorescent light along with chromophores present in a gel to produce photons at different wavelengths to penetrate deeper in the skin to influence biological activity, promote cutaneous repair, and increase antimicrobial activity. It has been shown to be successful as monotherapy for superficial pyoderma when compared to systemic antimicrobials for resolution of clinical lesions and to decrease the treatment time required (18).

Systemic therapy

Systemic antimicrobial therapy for superficial pyoderma is currently recommended to be 21 days or 1 week past resolution of clinical lesions, whilst deep pyodermas are recommended to be treated for 6 weeks or 2 weeks past clinical resolution. These recommendations are being evaluated further and may change in the future. Deep pyoderma necessitates systemic therapy, since topical therapy is unlikely to reach the infected area. Since antimicrobial stewardship is a major focus, guidelines regarding antimicrobial selection for superficial pyoderma have been developed, divided into tiers **(Table 1)**. First-tier antimicrobials are recommended as empirical therapy when culture has not been performed. Third-generation cephalosporins are placed into a gray area of first/second tier, due to the concerns of increased selection of antimicrobial resistance of gram-negative microbes at distant sites. Second-tier antimicrobials should not be used unless a culture has been undertaken, with susceptibility that shows it would be an appropriate choice. Third-tier antimicrobials should not be used unless there is no other option for treating the infection, as they are reserved for human medicine. Since superficial pyodermas can be treated topically, third-tier antimicrobials are not recommended in this situation; deep pyoderma, which requires systemic therapy, would be the only situation where these may be applicable (1).

One study looked at the temporal changes of antimicrobial resistance between 2010 and 2021 in the United States. They found a significant increase in resistance to clindamycin, amoxicillin-clavulanic acid, oxacillin, cefoxitin, cefpodoxime, tetracycline, chloramphenicol, erythromycin, marbofloxacin, and gentamicin. The only two antimicrobials evaluated which did not show an increase over that period were cephalothin and sulfonamides (10). This shows the need to follow antimicrobial stewardship guidelines and use systemic antimicrobials judiciously, as noted in the tier structure.

Carrier status

When pyoderma has been resolved, it is important to note that there is a high chance that the normal flora will then be the same organism that was treated; one study reported almost half (45.2-47.6%) of dogs with a pyoderma due to MRSP then had MRSP detected either on the skin or carriage sites after resolution of the infection (19). Almost as alarming is when dogs with pyoderma due to MSSP were treated successfully, 38.3% had MRSP detected on the skin or carriage sites afterwards (19). Trying to decolonize dogs infected with MRSP, as is performed in humans with MRSA, is not successful. Additionally, asymptomatic in-contact dogs have been shown to be positive at a similar frequency as dogs infected with MRSP (67.4% vs. 66.7%), demonstrating the transmission potential of bacteria with in-contact dogs in the house (20). Carrier status of MRSP was noted intermittently up to 10 months afterwards in this study, justifying the reason to culture an animal infected with a pyoderma if it has a history of MRSP within the last year.

Preventing recurrent pyoderma

Pyoderma is a secondary disease in most cases, so the primary disease must be evaluated and controlled to prevent recurrence of pyoderma (1). Atopic dermatitis is a common primary precursor for pyoderma in dogs, and in such cases treatment should shift to control the atopy in order to prevent excessive use of antimicrobials. An Australian study looked at dogs with atopic dermatitis which were

treated with oclacitinib; when compared to control dogs, fewer antimicrobial courses were prescribed in the oclacitinib treated dogs (21). Diet can also be beneficial to prevent pyoderma and lessen recurrence and severity of clinical signs from atopic dermatitis; one study in affected dogs fed an appropriate diet showed a significant decrease in signs of atopic dermatitis over a 9-month period (22).

Zoonotic concern

When managing any pyoderma, a common concern of owners is the zoonotic potential. There is a definite risk of bacteria being transferred from a pet to the owner and vice versa (1). A study in Taiwan showed an increased risk of owners being colonized with *S. pseudintermedius* when they have three or more dogs, and if they allow the dog to lick the owner's face (5). If the owners are colonized with MRSP from the animal, the genetic mutation from the MRSP could then be transferred to the owner's normal *Staphylococcus* spp. flora, which could mean that they are then at risk for MRS infections (7).

CONCLUSION

Bacterial resistance is significantly increasing with pyoderma. Therefore, topical therapy should be considered as the first line of treatment to prevent further pressure on the bacteria to develop resistance to systemic antimicrobials. If systemic antimicrobials are necessary, following the tier system is crucial; Tier 1 antimicrobials are ideal for empirical therapy, but Tier 2 antimicrobials should only be used when a culture indicates susceptibility.

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MANAGING SKIN DISEASE WITH FLUORESCENCE BIOMODULATION

The concern over increasing bacterial resistance to antibiotics has prompted clinicians to seek novel alternatives for conditions such as pyoderma; this article reviews the possibilities with one such treatment.

KEY POINTS

1. Fluorescent Biomodulation (FBM) is a form of laser therapy that is starting to show promising results in treating a variety of skin disorders in dogs.
2. Studies have shown that FBM downregulates pro-inflammatory cytokines and upregulates anti-inflammatory cytokines in the skin.
3. FBM in conjunction with systemic antibiotics can accelerate the improvement of canine pyoderma, and may be advantageous for treating other conditions such as perianal fistulae and otitis externa.
4. The technique is safe and appears to have good antibacterial efficacy, but its exact mode of action remains unknown.

Introduction

Fluorescence biomodulation (FBM) is a form of low-level laser therapy (LLLT) that is now gaining in popularity as a viable option for treating certain conditions in veterinary medicine. In general, LLLT methods typically employ photons of various wavelengths and operate at non-thermal irradiance levels to influence biological processes (1). To do this, light must be able to penetrate tissues, with the depth of penetration being dictated by the light's wavelength. The skin contains a variety of endogenous chromophores (molecules that absorb photons at certain wavelengths), the most common being hemoglobin and melanin; each has distinctive scattering and absorption coefficients that are significantly dependent on the wavelength of light (2). Therefore, the choice of wavelength is considered one of the most important factors in LLLT. With a FBM system, a blue LED light **(Figure 1)** is used to activate a substrate, a photoconverting gel containing chromophores **(Figure 2)**. The activated chromophores release energy in the form of fluorescent light which penetrates the patient's skin; the depth of penetration varies depending on the emitted spectral profile (2). Light in the blue-to-green

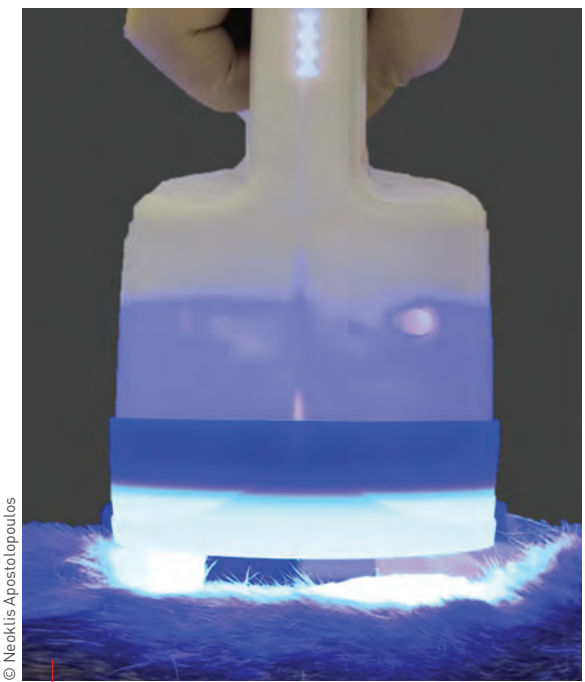

Figure 1. An example of a commercially available blue LED lamp for FBM.

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spectrum has a penetration depth of approximately 1-2.5 mm into the skin, primarily affecting the epidermis and the upper layer of the dermis. Red light can penetrate nearly 5 mm into the skin, reaching deep into the dermis, and possibly even the panniculus (2). This short article provides an insight into the use of FBM therapy for some skin conditions in clinical practice.

FBM in veterinary medicine

FBM was originally utilized in human medicine and is being now employed in veterinary medicine to treat various dermatological disorders, which are of course one of the most common reasons for pet owners to seek veterinary advice (3). At least one commercially manufactured system is now available for use in veterinary practice in many countries. The treatment duration is short, non-painful and can usually be performed without sedation. The process is simple; the area requiring treatment is first clipped (if necessary) and then cleaned with sterile saline before the chromophore gel is applied to a depth of approximately 2 mm with a spatula. This is then illuminated with the LED lamp for two minutes. Studies evaluating FBM have demonstrated the downregulation of pro-inflammatory cytokines and upregulation of anti-inflammatory cytokines. Growth factors that are important for proliferation of new granulation tissue, angiogenesis, and collagen remodeling – which together promote full wound healing – have been shown in studies to be elevated following treatment (1,2,4).

Pyoderma

FBM has been applied with promising results to treat both superficial bacterial folliculitis (5) and deep pyoderma in dogs (6). These studies show the technique is safe and can be used in conjunction with systemic antibiotics to accelerate the treatment of canine pyoderma. For superficial canine pyoderma, FBM could be considered for use as a sole treatment (1,2,5,7), although further studies are needed to prove this suggestion. **Figure 3** shows a dog with pyoderma of the vulva fold before treatment commenced. The pyoderma was treated with FBM at weekly intervals (with two consecutive applications per session) for two months, and the beneficial effects can be seen in **Figure 4**.

Figure 2. A commercially available photoconverter gel mixed with chromophores (orange liquid) which is applied to the area requiring treatment.

A prospective, randomized, and blinded clinical study assessed the efficacy of a FBM system to treat dogs with interdigital pyoderma. 36 dogs were randomly allocated to treatment groups of either antibiotic alone or antibiotic plus FBM application, with dogs in the latter group receiving the light treatment for two minutes twice a week until clinical resolution. Dogs were scored over a 12-week period, and the mean time-to-resolution of lesions was 4.3 weeks for those receiving both forms of therapy, as compared to 10.4 weeks for dogs that received only antibiotics. The conclusion was that FBM significantly reduced the time needed for clinical resolution (8). FBM twice weekly can, therefore, be recommended as a therapeutic approach for managing interdigital pyoderma in dogs (9); treating affected dogs once weekly (with two consecutive applications in the same session) could also be considered as an option (10), but larger randomized studies are needed to validate the existing suggestive data (9).

While these results show the clinical antibacterial efficacy of FBM, the mechanism remains unknown; two preliminary *in-vitro* studies were unable to demonstrate bactericidal activity of FBM (11) or blue LED light (12).

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Figure 3. A dog with pyoderma on the vulva folds before treatment. Note the erythema, the exudation, and the erosion of the skin.

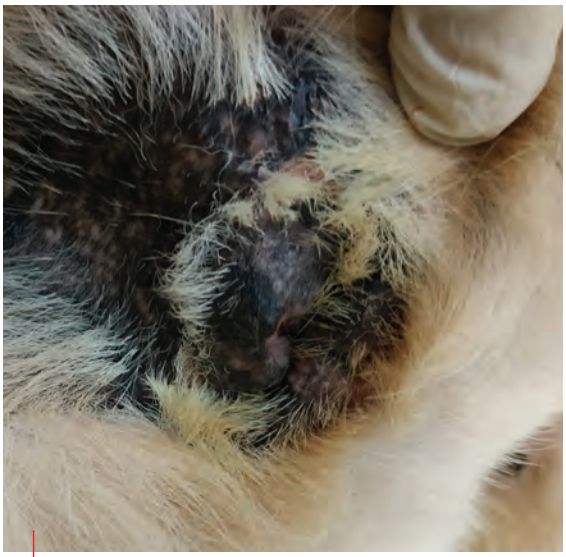

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Figure 4. The same case as **Figure 3**, two months after treatment with FBM once weekly (two applications per session).

Otitis externa

A randomized non-blinded clinical trial suggested that FBM could also be beneficial in the treatment of otitis externa in dogs (13), a common condition accounting for up to 20% of consultations in small animal practice (14). Application of FBM in the external ear canal may modulate inflammation, pain and bacterial growth (13) – although as mentioned above, *in-vitro* studies have not been able to determine why FBM or blue LED light should have bactericidal activity. However, in contrast, a preliminary *in-vitro* study has shown that FBM can inhibit the growth of *Malassezia pachydermatis* after at least four minutes of exposure (15).

Miscellaneous skin conditions

Another reported application of FBM is for canine perianal fistulae (16). In this study, four dogs with the condition were treated solely with FBM once a week, with two consecutive applications at each session. After two weeks of treatment all dogs had improved, with a significant reduction in vocalization, straining, and licking, and the perianal lesions were significantly decreased after five weeks of therapy. Again, the mechanism as to how FBM helped in these cases remains unknown. **Figure 5** shows a case of canine perianal fistula before treatment with a commercially available FBM system once weekly. Three weeks after the

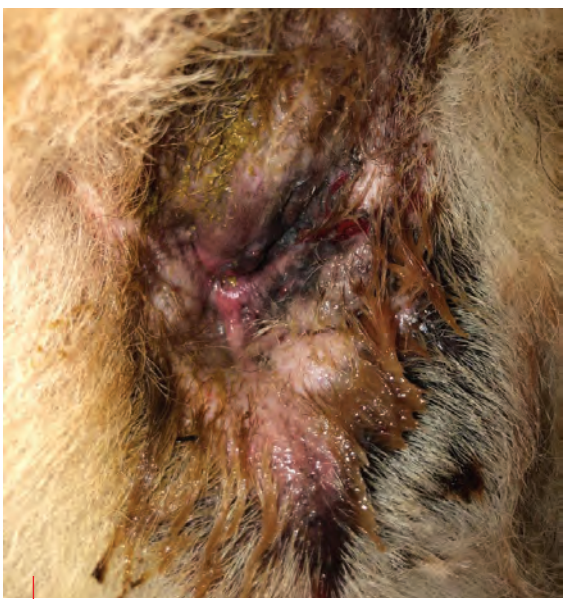

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Figure 5. A dog with a perianal fistula before FBM treatment. The patient was treated with FBM once weekly (two applications per session).

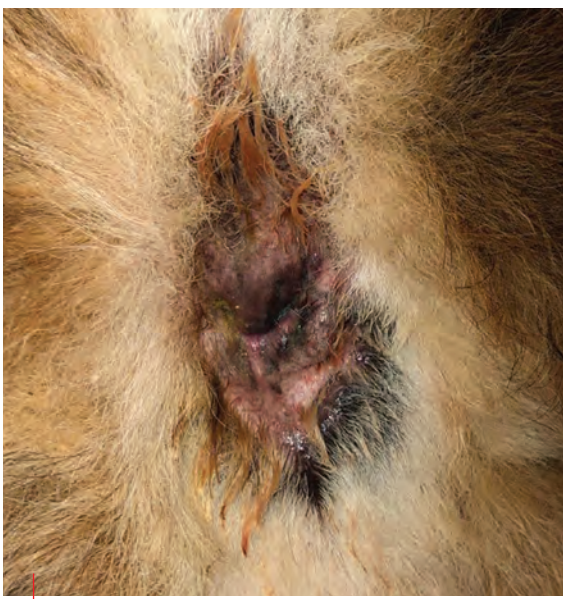

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Figure 6. The same case as **Figure 5**, three weeks after the first treatment.

first treatment there was reduction in the erythema and improvement of the fistula **(Figure 6)**. It is, therefore, speculated that the effects of FBM on wound healing might be beneficial in such cases (1-3).

It is important to mention that many of the above conditions result from underlying diseases, such as atopic dermatitis, cutaneous adverse food reactions, ectoparasites, endocrine disorders and conformational problems. It is essential that wherever possible the underlying disease should be identified with a proper work-up (skin scrapes, cytology, blood tests, elimination diet, etc.) and properly addressed.

Finally, FBM has been reported to aid healing of acute uncomplicated surgical wounds (3); FBM therapy has been shown to stimulate the release of promoting wound-healing cytokines and improve the microscopic characteristics of incisional wounds. Tissue re-epithelization was complete, with better collage deposition and less dermal inflammation. However, the macroscopic appearance of the wounds was not affected by FBM (3) and further, larger studies are needed to evaluate these results (9).

"FBM has been applied with promising results in treating both superficial bacterial folliculitis and deep pyoderma in dogs."

Neoklis Apostolopoulos

CONCLUSION

These promising findings suggest that FBM can be used to treat several canine dermatological disorders and that there is the potential to expand its applications in veterinary medicine. Further studies are, however, needed to evaluate the efficacy of the modality in treating different skin diseases and to reveal its exact mechanism of action.

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CHRONIC CANINE OTITIS: PREVENTION IS BETTER THAN CURE

Otitis is a common problem in dogs, and can quickly become chronic if prompt and appropriate action is not followed; this article discusses how best to approach these cases.

KEY POINTS

1. Certain primary factors in individual dogs can affect the ear canal and cause otitis; these include atopy, foreign material in the ear, adverse food reactions and parasites.
2. Various predisposing factors may contribute to chronic otitis, such as particular anatomical features, excess swimming, and disproportionate cerumen production.
3. Appropriate early investigation and treatment can prevent acute otitis from becoming a recurrent or long-term problem.
4. In some cases, long-term therapy or surgical intervention is necessary to manage the condition.

Introduction

Describing a clinical condition as "chronic" can mean that it has a prolonged time course, that definitive healing is impossible, or that the underlying cause is persistent. Any of these definitions can apply to otitis (1) when treatment has been ineffective due to insufficient control of the primary cause of the disorder, or because there is a perpetuating element that has not been detected or has not been adequately resolved (2). This article will review why the canine ear is predisposed to otitis, and what can be done to minimize the risk of an ear problem becoming chronic.

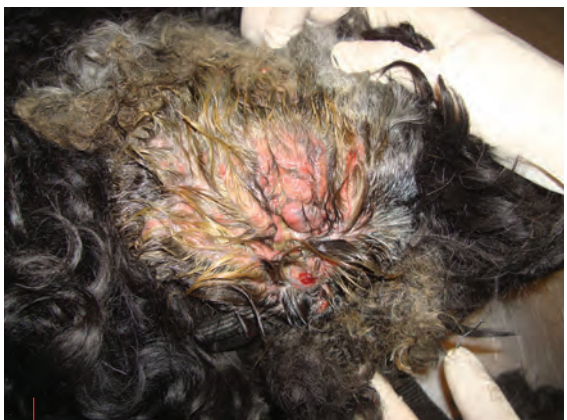

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Figure 1. Purulent otitis with a severely ulcerated ear canal.

Firstly, it should be said that the anatomical structure of the ear in itself favors dysbiosis of the microbiome, as intertrigo (inflammation caused by the rubbing of one area of skin on another) problems can easily develop, and its "anti-gravitational" conformation discourages drainage (3,4) **(Figure 1)**. However, not all cases of otitis will necessarily lead to dysbiosis, and in some situations abundant cerumen production and itching can be taken to constitute otitis. In addition, secondary agents **(Figures 2 and 3)** will proliferate when the ear's defense and microbiome controls fail, as can be seen from cytological studies (5,6); indeed, cytology must be undertaken for all cases of otitis in order to establish a firm diagnosis, and some tips are given in **Table 1**.

What causes acute or chronic otitis?

The most common mistakes made by veterinarians, and which may lead to otitis becoming chronic, include:

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- Suspending treatment based only on clinical improvement, without cytological confirmation.
- Using antibiotics at random without first obtaining an antibiogram.
- Failing to perform thorough cleaning despite adequate antibiotic treatment.
- Failing to proactively treat the primary cause of the otitis, thereby facilitating recurrence.
- Being limited in treatment options because of economic or logistical issues (*i.e.*, cost or the prolonged nature of therapy).

It is, therefore, very important to remember the causes that underlie altered ear homeostasis which can give rise to acute inflammation; if not effectively controlled, these can result in structural changes to the external canal and/or middle ear, and perpetuation of the problem (2). All studies on canine otitis mention certain factors inherent to affected patients and which predispose to the condition. Such characteristics are commonly found in the canine population and will favor the development of otitis (7); they include (from greatest frequency):

- Atopic dermatitis
- Foreign bodies (grass fragments or ceruminous otoliths)
- Adverse food reactions
- Infestation due to *Otodectes cynotis* (ear mites)
- Polyps and tumors of the external auditory canal
- Adverse reactions to topical ear medications
- Endocrine disease
- Primary seborrheic disorders
- Transient ecosystem changes (due to inadequate care)
- Aural demodicosis (or other less frequent parasites)
- Aural dermatophytosis

Apart from these primary causes, the presence of predisposing factors may contribute to chronicity of the problem, since they favor recurrence and complicate treatment, causing the latter to be less effective. These include:

- Frequent swimming
- Conformational conditions such as a narrow, long, deep and/or hairy auditory canal
- Excessive cerumen production due to idiopathic causes
- Drooping external ears/pinnae

When otitis appears, the microenvironment conditions within the ear change, due to an increase in cerumen production and narrowing of the canal induced by the inflammatory process. This inevitably

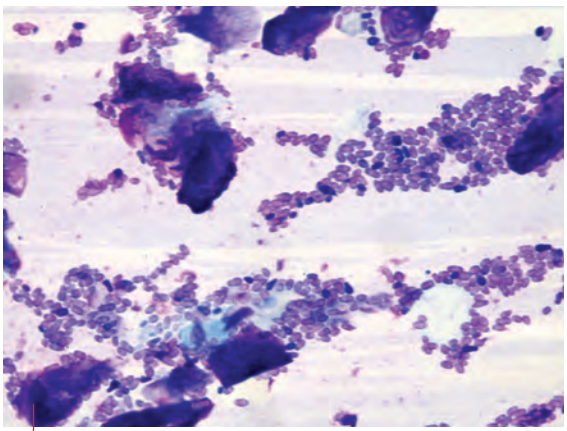

Figure 2. Cytology from a dog with chronic allergy showing a *Malassezia* biofilm (x40 magnification).

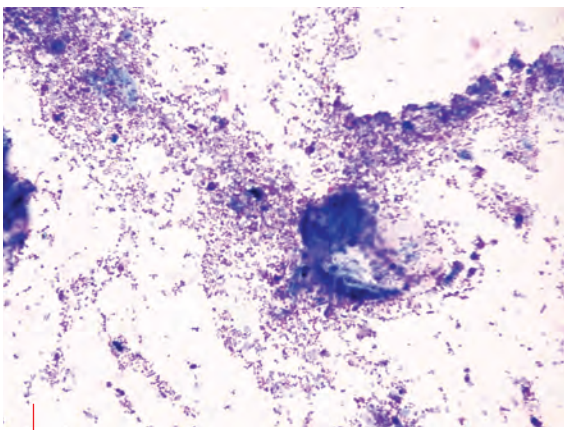

Figure 3. Cytology from a dog with chronic otitis showing overgrowth of cocci (x10 magnification).

Table 1. Some tips for interpreting cytology from ear swabs.

• *Malassezia* usually appears in the absence of inflammatory cells **(Figure 2)**.
• Cocci usually induce a neutrophilic inflammatory response, although in some cases they may appear surrounded by a ceruminous matrix **(Figure 3)**.
• *Pseudomonas* and *Proteus* spp. normally induce a severe neutrophilic inflammatory response.
• *Corynebacteria* spp. may be present together with other bacteria or as a single population. However, as bacilli, they are less pathogenic than *Pseudomonas* or *Proteus* spp., and are easier to treat with traditional topical agents.

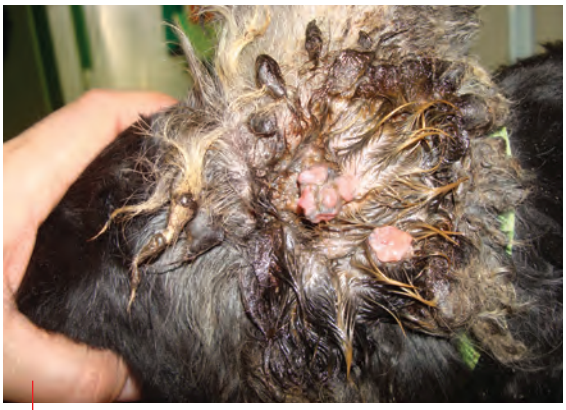

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Figure 4. Chronic purulent otitis with polypoid hyperplasia of the pinna.

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Figure 5. Hyperplasia of the external ear with severe stenosis of the canal secondary to chronic otitis.

leads to alteration of epithelial migration, resulting in dysbiosis of the microbiome. If this is not quickly resolved, the changes may persist, causing the otitis to become chronic **(Figure 4)**.

Most cases of otitis start with the appearance of aforementioned primary factors, and failure to resolve the problem may lead to persistence due to various conditions developing subsequently (8). These can include:

- The favoring of resistant bacterial strains due to incorrect treatment.
- Eardrum rupture from enzymes secreted by invasive bacteria.
- Perpetuation of the infection due to unresolved otitis media.
- Hyperplasia, fibrosis, narrowing and calcification of the auditory canal over time **(Figure 5)**.
- The accumulation of cerumen (otoliths) that obstruct epithelial migration and sequestrate bacteria.
- The organization of microorganisms into treatment-resistant biofilms.
- Excessive or irritating ear cleaning, which may favor inflammation.

Preventing acute otitis from becoming chronic

Primary causes

If the primary cause can be identified, this will aid in selecting the most appropriate treatment.

- **Atopic dermatitis:** This disease clearly induces an imbalance in the ear's microenvironment. The cerumen of affected dogs may fail to control the microbiome, not only due to its excess production secondary to inflammation, but also because of a deficiency in defensins (host defense peptides). Avoiding relapse in the form of outbreaks that can disrupt the microenvironment is crucial in order to prevent ceruminous otitis with or without dysbiosis from repeating. Each individual requires a personalized strategy, but proactive measures with systemic medication are recommended, for example monthly lokivetmab injections, daily oclacitinib or cyclosporine at maintenance doses, corticosteroids at pulse dosing (*e.g.*, twice weekly), or anti-fungal azoles (again pulse dosing). Topical treatment may also be appropriate for some cases; these include corticosteroid preparations, antiseptic agents, anti-fungal azoles, or cerumenolytic agents to keep the canal clear, all administered once or twice a week. Topical corticosteroids can control inflammation and the toxic negative effects of excess cerumen, allowing the microbiome to exert its protective function correctly; in many cases dysbiosis can be controlled without the use of antiseptics or antibiotics.

- **Foreign bodies:** Clinical experience shows that there are cases of otitis in which a foreign body or an otolith has remained lodged for a long period of time, and is only discovered when performing otoscopy under sedation or general anesthesia. A thorough evaluation of the ear is, therefore, highly recommended in order to rule out any possible obstruction of the canal or to detect the presence of excessive post-inflammatory cerumen.

- **Adverse food reactions:** Failure to identify a dietary allergen may give rise to or perpetuate otitis, causing it to become chronic. When following a diagnostic protocol with a relapsing otitis, this possibility should be examined via the use of an elimination diet.

- **Ear mites:** In recent years the introduction of macrocyclic lactones and isoxazolines as routine external antiparasitic agents has caused otoacariasis to become infrequent. However, the diagnosis is relatively simple and is based mainly on the type of cerumen produced.

- **Polyps and tumors:** Polyps develop mainly as a consequence of chronic irritation, whilst various different tumors can be found in the ear canal. Any growth will hinder epithelial migration and favor chronic dysbiosis. When they involve the middle ear, these lesions may be more difficult to diagnose, and can contribute to ongoing inflammation or chronic infection in the area.

- **Adverse reactions to topical products:** Worsening of otitis signs following topical treatment may be indicative of an adverse contact reaction to the drug employed. These will typically appear shortly after application of the product, with severe erythema and exudation developing, mainly at the entrance to the canal.

- **Endocrine disease:** hormone abnormalities, especially hypothyroidism but also hyperadrenocorticism or altered sex hormones, can adversely affect cerumen secretion and favor dysbiosis, with the subsequent development of varying degrees of otitis.

- **Primary seborrheic disorders:** These are more common in some breeds of dog and can alter the ear ecosystem due to changes in the quality and amount of cerumen **(Figure 6)**.

- **Transient ecosystem changes:** In patients that are susceptible to otitis due to the presence of one or more primary causes, inappropriate cleaning or esthetic care may serve as a trigger to induce or perpetuate otitis. For example, plucking intra-auricular hairs, excessive or very irritating cerumenolytic use, or the use of swabs can all facilitate ecosystem imbalance (8).

- **Otic demodicosis:** Nowadays this condition is rare, and as with *Otodectes*, newer antiparasitic medications have caused it to become even more unusual. However, the presence of *Demodex* mites in the outer ear alone may be considered, and will always be a possibility in dogs that have been treated for parasites with substances other than macrocyclic lactones or isoxazolines.

Predisposing factors

When it comes to predisposing factors, certain measures can be taken to prevent otitis from becoming chronic (9). For instance:

- **Frequent swimming:** Avoiding this habit altogether may be a good option; however, if it proves difficult, the use of topical antiseptics or pH acidifiers applied to the ears when the dog comes out of the water may help counter the development of dysbiosis.

- **Conformational conditions:** Certain breeds have anatomical characteristics that predispose to otitis; the Shar Pei is most commonly implicated. Clinical experience has shown that if no intervention is necessary, it is best not to use cleaning agents in their ears. Where a primary anatomical cause induces acute inflammation, keeping the ear canal clear can be difficult, and in many situations it will be necessary to apply topical corticosteroids and cerumenolytic agents on a regular basis.

- **Hairy auditory canals:** Again, this is often a breed-specific problem – *e.g.*, in the Bichon Frise. Otoscopy will show hair extending to the periphery of the tympanic membrane. In these dogs, although keeping the canal clear may require removal of the hair, where a primary cause is present, it may be better to avoid this practice in order to avoid follicular microtrauma.

- **Narrow, long or deep auditory canals:** These features are one of the most important causes contributing to the complication of otitis, and again can be breed-specific (*e.g.*, the German Shepherd dog); for example, a long canal increases detritus accumulation and makes it more difficult to remove.

- **Excessive cerumen production:** In some breeds or individuals, excessive cerumen may be directly related to generalized seborrhea, and it is not always easy to determine the cause. These patients will need regular application of cerumenolytic agents and topical corticosteroids to reduce the amount of cerumen produced.

- **Drooping external ears:** Pinnae that cover access to the ear canal can complicate all treatments and prevent moist and detritus-laden ears from aerating and releasing these products.

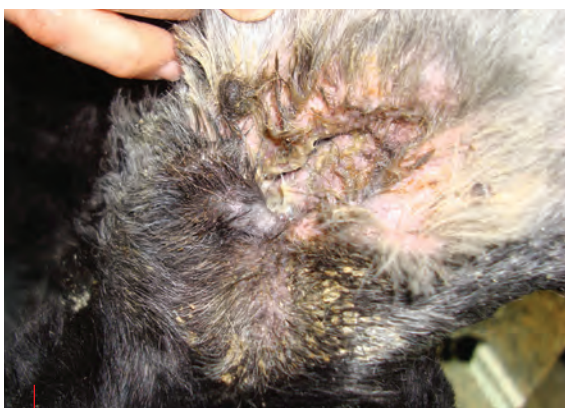

Figure 6. Otitis in a Cocker Spaniel secondary to severe seborrhea.

Perpetuating factors

The above recommendations can serve both to avoid otitis and to prevent it from repeating or becoming chronic. However, it is important to take into account that recurrence sometimes cannot be avoided due to the existence of perpetuating factors. Three main ones have been identified: biofilm formation, otitis media, and narrowing, fibrosis and calcification of the ear canal.

- **Biofilm formation**

Both yeasts and some bacterial strains (mainly *Pseudomonas* spp.) can organize into a layered formation along with glycoproteins and air and fluid distribution channels that are resistant to traditional cleaning practices and antibiotics, thereby allowing perpetuation **(Figure 7)**. It is known that the bacterium *Finegoldia magna* in the external auditory canal is an opportunistic anerobic

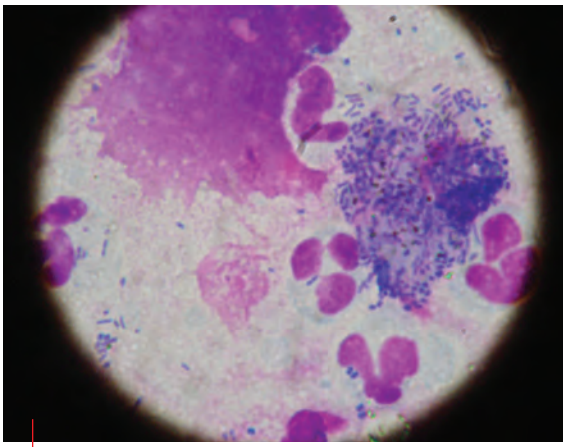

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Figure 7. Cytology from a dog with severe otitis showing a biofilm of cocci and bacilli (x10 magnification).

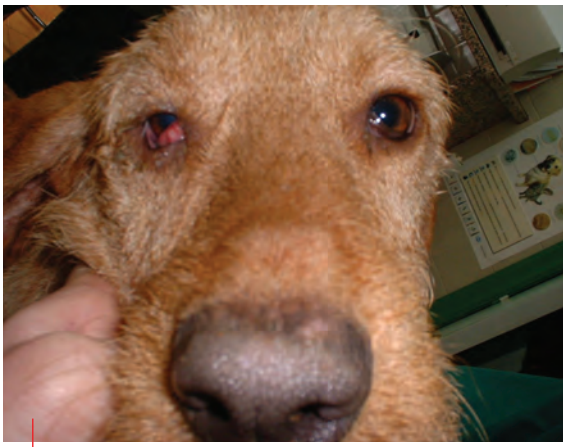

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Figure 8. Horner's syndrome in a dog caused by otitis media.

pathogen that facilitates *Pseudomonas* biofilm formation (10). It is sometimes not easy to identify biofilm, although there are some features suggestive of its presence, such as a dark, sticky, and bright mucoid secretion that does not adequately respond to treatment. Although biofilm can be reduced with treatment, microorganism overgrowth is never fully controlled.

Acetylcysteine and Tris-EDTA may serve to disrupt the biofilm, mainly by acting on the sulfur bonds that stabilize it. In the presence of an intact eardrum, liquids with potent cleaning action, such as carbamide peroxide, can also be used. According to some studies, enzymatic cleaning agents such as lactoferrin, lactoperoxidase and lysozyme may be effective in cases of otitis with resistant strains. New Burow's solution (based on 2% aluminum acetate and 0.1% betamethasone) may be indicated in cases of otitis media with infection due to multi-resistant strains (11). Another option is video-otoscopy under general anesthesia to perform circular brushing using a pump and saline suction (12).

- **Otitis media**

Middle-ear problems are a common complication of chronic otitis, particularly when gram-negative bacteria such as *Pseudomonas* spp. are present (13). The proteolytic enzymes released by these bacteria can rupture the eardrum, spreading the infection and the inflammatory products into the middle ear. A biofilm may also develop at this site, sometimes affecting the tympanic bulla and generating a situation that considerably complicates the prognosis (1,14). Cytological study is fundamental in all patients with otitis media, and differentiation between cocci and bacilli can greatly guide the steps to be taken (15,16). It is very important to take into account that in allergic dogs, *Malassezia* overgrowth may perpetuate chronicity, and in some cases can prove very difficult to treat, partly again as biofilm formation may be involved (1,14-16). In addition, although culture and an antibiogram are essential in these circumstances, sometimes there is no direct relationship between the *in-vitro* and *in-vivo* findings of these tests (1,5,9,10). Experience shows quinolones to be the safest antibiotics to use where there is a ruptured tympanic membrane, and they usually exhibit a broad spectrum of action. The use in the mornings of a combination of cleansing fluid composed of Tris-EDTA and/or n-acetylcysteine is usually the preferred method for eliminating inflammatory debris, rupturing the biofilm and sensitizing the bacteria to the antibiotics that will be administered afterwards.

Suspicion of otitis media with a ruptured tympanic membrane may be raised by a number of signs:

- Coughing or swallowing at the time of washing.
- Pain on pressing the throat near the bulla.
- The formation of bubbles when washing and flooding the external ear.
- Deeper penetration of a probe when comparing the healthy ear to the ear with the ruptured eardrum.
- Presence of neurological signs **(Figure 8).**
- Otitis unresponsive to treatment and which shows some opacification of the lumen of the bulla or wall thickening on radiography.

However, the best diagnostic images can be obtained with magnetic resonance imaging or computed tomography (17).

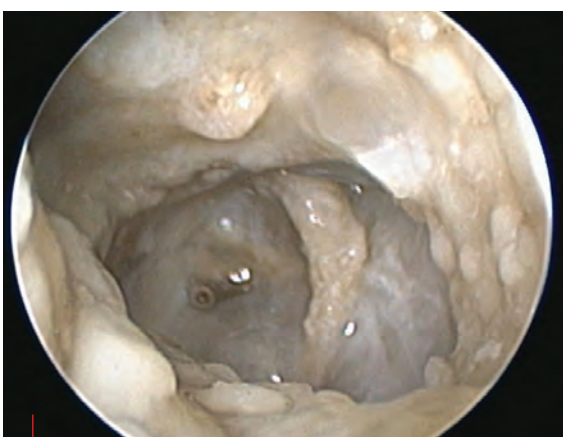

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Figure 9. Otoscopy showing otitis due to aspergillosis infection.

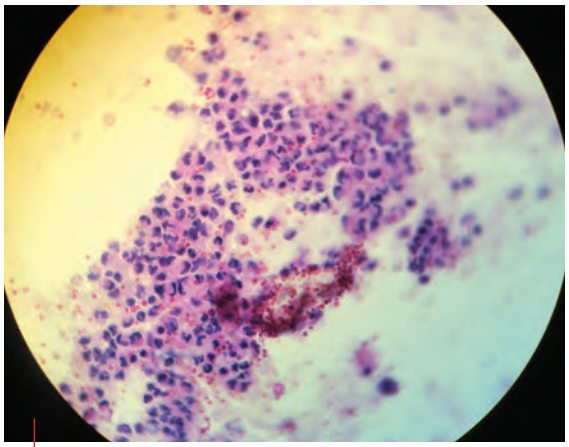

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Figure 10. Cytology from the dog in **Figure 9** revealed aspergillosis spores (x10 magnification).

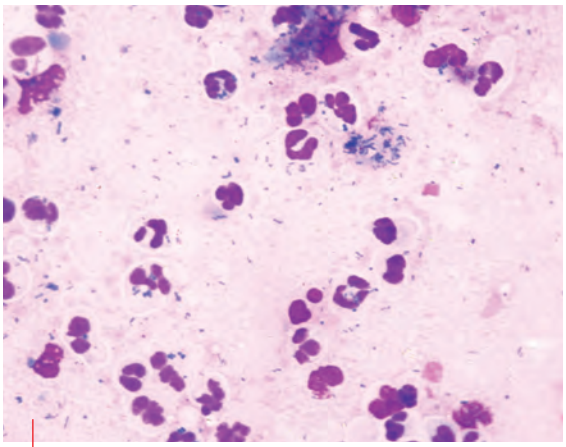

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Figure 11. Cytology from a dog with otitis demonstrating bacilli and degenerated neutrophils (x40 magnification).

- **Alterations to the ear canal**

Chronic inflammation of the ear canal, including the dermis and the cartilage of the external ear, causes the tissues to fibrose, with the accumulation of calcium salts that result in a rigid and irreversible structure. In the early stages, or before the calcium accumulates, when narrowing is due mainly to edema of the canal's subdermal layer, systemic corticosteroids at immunosuppressive doses for 15 days may be used in an attempt to reverse the stenosis and allow restoration of epithelial migration (14). In addition, 0.1% mometasone cream or lotion applied topically may help open the ear canal.

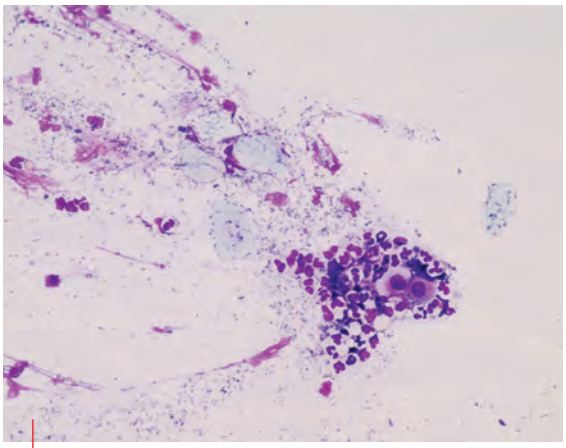

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Figure 12. Cytology from a dog with otitis showing bacilli (x10 magnification).

Managing patients prone to relapse

There are situations in which the balance of the ear's ecosystem is very sensitive to relapse, or the structural changes are so serious that restoration of epithelial migration is impossible and the options for avoiding ablation surgery are minimal. In some circumstances pulse-based therapy is inevitable, such as where:

- Cytology persistently shows microorganism overgrowth with abundant cerumen and keratinocytes.
- The ear canal lumen remains narrow, and cleaning cannot be easily achieved.
- The tympanic membrane fails to heal, and cytology of the middle ear continues to show the presence of microorganisms, even if no inflammatory cells are observed.

Pulse-based treatments usually involve effective cerumenolytic agents combined with antifungal drugs and antiseptics to control overgrowth and prevent proliferation. In some cases, corticosteroids (*e.g.*, hydrocortisone aceponate) can help, and may be a good way to avoid excessive cerumen production and secure reduced levels of inflammation (18). Conditions that prove difficult to treat may arise in some patients with chronic otitis overtreated with antibiotics and which ultimately suffer invasion by fungal organisms such as

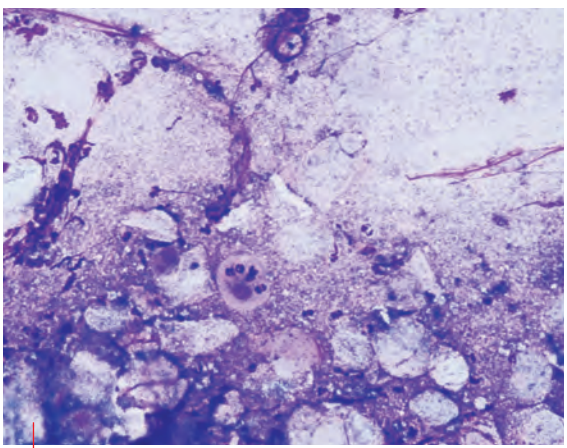

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Figure 13. Cytology from a dog with severe chronic purulent otitis that proved difficult to resolve (x10 magnification).

Aspergillus spp. These cases are characterized by ulceration and other severe signs, and require thorough cleaning and intensive therapy with antifungals such as azoles via both topical and systemic routes (14) **(Figures 9 and 10)**.

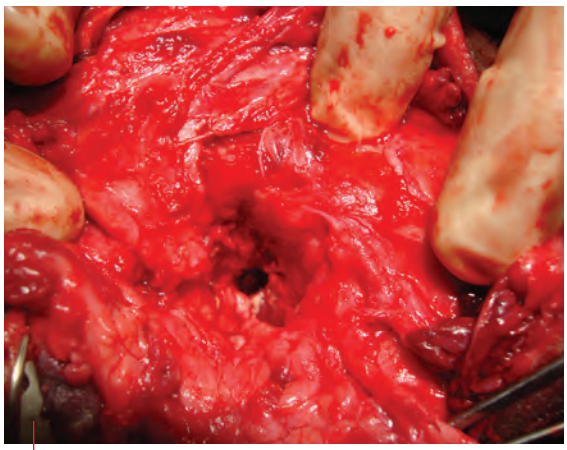

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Figure 14. An intra-operative image showing exposure of the tympanic bulla for curettage.

In other cases, healing is impossible because of terminal situations such as perpetual biofilms that do not respond to treatment **(Figures 11-13)** or where stenosis of the ear canal is so severe that anti-inflammatory medication proves ineffective. When the restoration of epithelial migration is not possible due to irreversible structural changes, there may be no option other than surgical exposure of the ear canal and ablation of the bulla with curettage **(Figure 14)** in order to avoid relapses **(Table 2)**. However, surgical measures are not always a definitive solution, since in some cases the primary causes continue to act on small areas of epithelium of the residual canal. Owners must understand that surgery should always be the last option, and the clinician should be aware that this measure may be interpreted as a failure of the previous prescribed medical treatment.

Table 2. Surgical options for chronic otitis externa (1,14,19,20).

Lateral wall resection, for: • Cases of poor ventilation due to drooping external ears • Cases of poor ventilation due to narrow ear canals • Cases of poor ventilation due to very hairy ear canals • Seborrheic otitis without medical control • Cerumen gland hyperplasia in the vertical canal • Fibrosis of the vertical canal due to unresponsiveness to treatment • Neoplasia of the vertical canal
Total ablation of the ear canal and osteotomy of the bulla, for: • Persistent or refractory otitis media • Osteomyelitis of the bulla • Fibrosis of the horizontal canal • Calcification of the horizontal canal • Neoplasia of the horizontal canal or bulla

CONCLUSION

Prevention is always better than cure, and nowhere more so than with otitis. The clinician should be aware of the primary causes of otitis and be able to identify dogs at risk due to the presence of predisposing factors. Appropriate and aggressive treatment, linked to careful cytological testing, should help minimize the chances of an acute otitis becoming chronic and possibly irreversible.

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DEMYSTIFYING THE BIOFILM IN CANINE OTITIS

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Biofilms can be a major concern when dealing with otitis externa infections; this article discusses why they are problematic, and goes on to consider how best to identify and effectively control them.

KEY POINTS

1. Biofilm formation plays a significant role in drug resistance with otitis infections.
2. Planktonic bacteria exhibit distinct physiological characteristics compared to those within a biofilm, which affects their virulence factors.
3. Biofilm formation can be observed in both monomicrobial and polymicrobial infections, involving not only bacteria but also fungi such as *Malassezia* spp.
4. Treatment options primarily focus on disrupting the biofilm to enhance the effectiveness of antibiotics against bacteria.

Introduction

Otitis is a common condition encountered in first-opinion veterinary practice, with allergy being the most common trigger in dogs. The inflammation of the ear canal can then lead to secondary overgrowth of bacteria or yeasts, and when left unmanaged, otitis can progress to a chronic condition. In such cases, perpetuating factors may come into play, for example the presence of otitis media, calcification of the ear canal, or changes in the ear's microbial flora, resulting in the emergence of more virulent strains of bacteria (1).

In certain cases, particularly when specific pathogens such as *Pseudomonas* spp. are involved, biofilm formation can be observed (1). Biofilm is a complex, living biomass with a specific structure that makes its elimination very difficult once established. Microorganisms within the biofilm employ various factors to make them more resistant to both the immune system and antibiotic treatment (2). This article aims to clarify the concept of biofilms, providing readers with the knowledge necessary to recognize their presence, thereby facilitating the implementation of appropriate treatment strategies.

What lies beneath: unraveling the mystery of biofilms

Biofilms are complex structures formed by the accumulation of microorganisms, creating a bacterial aggregate with a unique composition. A biofilm consists predominantly of water (90%), with the remaining 10% comprising the microbial biomass (2). Other than water, the main components of biofilm matrix are extracellular polysaccharides (EPS),

DNA and proteins. This combination of components imparts remarkable properties to a biofilm, which has significant implications for the survival and persistence of its bacteria (3).

The development of the three-dimensional structure of a biofilm occurs in several stages. Initiation begins with the attachment or adhesion of free-living bacteria, known as planktonic bacteria, to a surface. This attachment becomes irreversible, and the bacteria then undergo a transition to a sessile state. Subsequently, they aggregate to form a microcolony and initiate the production of the extracellular matrix by activating specific genes. Once the biofilm matures, fragments containing planktonic bacteria detach and disperse into the surrounding environment, facilitating biofilm dissemination (2). A notable advantage of biofilm formation is its ability to establish a gradient from the outermost to the innermost layers, in terms of nutrients, oxygen levels, growth rates, and genetics (4) **(Figure 1)**.

One of the key factors of bacterial biofilms is their ability to create a protective barrier that is resistant to antibiotics. Bacteria embedded in a biofilm are better protected against the effects of antimicrobial treatments, making biofilm-associated infections more challenging to eliminate (5). Furthermore, biofilms exhibit increased resistance to environmental stresses, including attacks by the host's immune system – for example, they can be resistant to phagocytosis by leukocytes (6). Another critical aspect of biofilms is their capacity for horizontal gene transfer. Due to the close proximity of bacterial cells within the biofilm, genetic exchanges can occur more efficiently, facilitating the dissemination of beneficial traits or antibiotic resistance within the bacterial population (7).

Quorum sensing (the ability to detect and respond to cell population density by gene regulation) plays a major role in the complex process that is biofilm formation. Essentially, quorum sensing allows bacteria to coordinate their behavior based on their cell density, enabling bacteria in a biofilm to synchronize the production of key components of the extracellular matrix, such as EPS (2).

Exploring biofilm formation: which organisms are involved?

Both Gram-positive and Gram-negative bacteria demonstrate the ability to produce biofilms. Among the bacteria commonly reported or observed to do so in canine ear infections, *Pseudomonas* spp. stands out as a frequent culprit, with a high incidence of biofilm production (8). Biofilms can be composed of a single organism, or may include multiple organisms, a phenomenon known as polymicrobial biofilm formation. This diversity in biofilm composition highlights the complexity of these structures and their role in various infections (9).

Among other species known for biofilm production, researchers in human medicine have identified *Staphylococcus epidermidis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Streptococcus viridans, Staphylococcus aureus*, and *Enterococcus faecalis (2)*. In veterinary medicine, biofilm-forming bacteria at sites other than from ear infections have been encountered, including, among others, *Staphylococcus* spp. and *E. coli* (10). And the concept of biofilm is not limited to bacteria alone; fungi such as *Malassezia* spp. also have the capability to form biofilms (11). This emphasizes the broader significance of biofilm formation across microbial species and underscores the importance of understanding and managing biofilms in various clinical and veterinary contexts. It also emphasizes that when dealing with biofilms, it is essential to not focus exclusively on *Pseudomonas* spp. but to investigate the possible presence of other microorganisms; pathogen

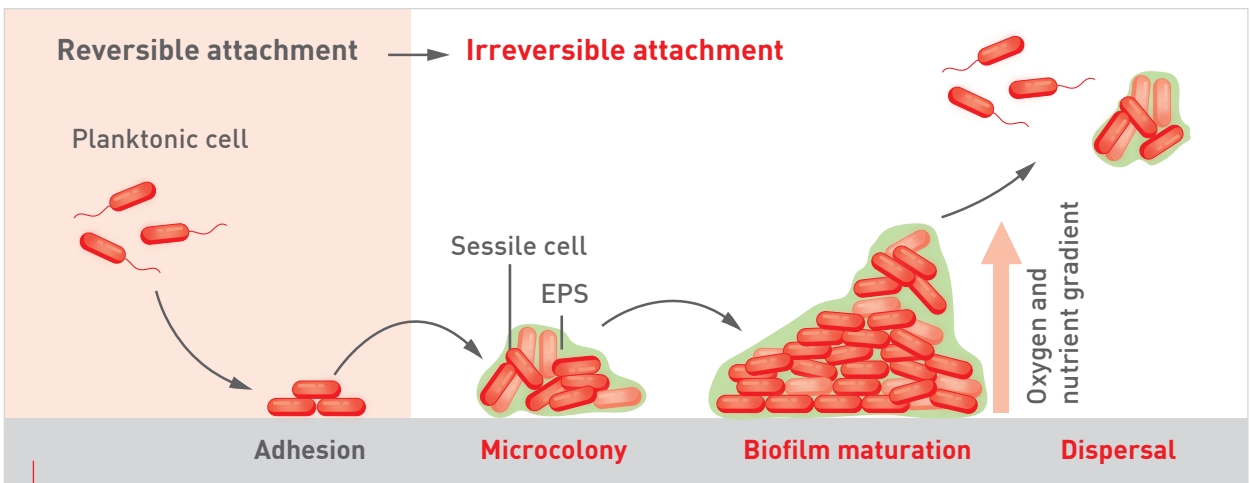

Figure 1. An example of the bacterial biofilm cycle, showing the different stages of the three-dimensional formation and dispersion. EPS: extracellular polysaccharides

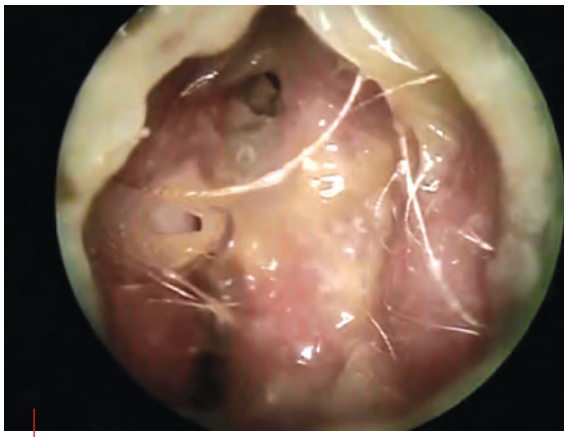

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Figure 2. A dog's external ear canal showing the presence of sticky exudate and chronic structural modifications.

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Figure 3. The same dog as in **Figure 2**, with extension of the exudate to the medial aspect of the right pinna.

identification is essential to optimize effective management of these infections. Biofilms can be complex communities comprising various species, making it crucial to adopt a thorough and multifaceted approach to address the diverse challenges they may pose by pinpointing the responsible pathogens.

The extent of bacterial biofilm production is often categorized on a scale of weak to strong, and depends on the bacterial or fungal strains involved (12); for instance, a study has highlighted that *Pseudomonas aeruginosa* is a strong biofilm producer compared to other species (13). This classification of biofilm production levels could potentially serve as a tool for assessing the potential virulence and treatment resistance of various bacterial strains, helping in clinical decision-making and therapeutic approaches, but it remains to be studied if it really could have a clinical and therapeutic impact (12).

Revealing biofilms: methods for detection and visualization

Detecting a biofilm can be challenging, as these structures are often not easily visible to the naked eye and require specific detection methods (14). Clinically, the macroscopic aspect of biofilms can vary depending on their maturity, the type of microorganisms involved, and what site in the body is involved **(Figures 2 and 3)**. Different characteristics can be observed (14):

- Color: can range from white/translucent to gray/green
- Texture: may appear slimy, sticky or mucoid
- Shape: can exhibit a flat or a three-dimensional aspect

A clinical observation in the case of *Pseudomonas* spp. infection is the appearance of a classic grayish/greenish, sticky, or slimy biofilm. This may be attributed to the presence of alginate, as well as the production of pyocyanin, which imparts these characteristics (15).

The cytological appearance of biofilms depends on the microorganisms involved and the sample preparation technique. Special stains such as Periodic Acid Schiff that highlight the polysaccharide matrix can be used, but these are generally not available in routine practice, making identification challenging (16). However, it is important to note that biofilms may appear as clusters of cells (bacteria, spores, fungal hyphae) surrounded by an extracellular matrix (which is not always visible) and may or not be accompanied by polymorphonuclear neutrophils or mononuclear cells (17) **(Figure 4)**.

Bacterial or fungal culture of microorganisms able to form biofilm is one of the diagnostic criteria for biofilm identification. However, it should not be considered a gold standard, as false negative cultures can be observed and discrepancies have been noted between bacterial culture and 16S amplicon profiling (18). Traditional culture methods primarily support the growth of planktonic bacteria, failing to accurately mimic biofilm conditions. Consequently, therapy decisions based on antibiograms derived from planktonic bacteria may not reflect the true antimicrobial susceptibility profile. Moreover, replicating biofilm conditions from planktonic

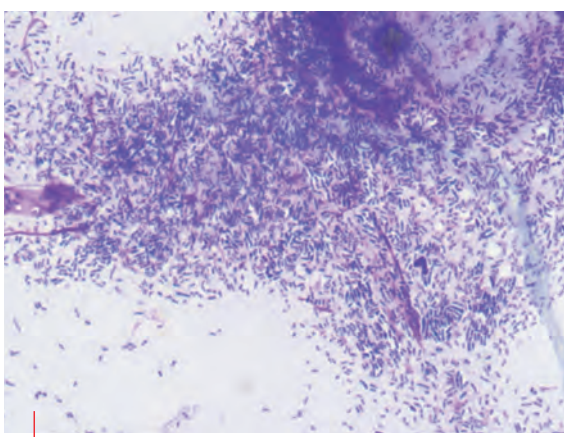

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Figure 4. Cytology of an otic sample containing biofilm from *Pseudomonas* spp. showing a high density of clustered microorganisms. 100X (oil) objective. (Diff Quick® Staining)

cultures can be challenging due to potential differences in biofilm maturity between the sampled and cultured bacteria. Bacteria within biofilms exhibit considerably higher antibiotic resistance compared to their planktonic counterparts, rendering antibiotic susceptibility assessments less predictive of treatment efficacy (15).

This limitation underscores the need for alternative methods, such as the Crystal Violet biofilm assay using broth media (*e.g.*, Luria-Bertani Broth, Mueller-Hinton Broth or Tryptic Soy Broth), to assess biofilm production based on optical density readings. These methods offer a more comprehensive understanding of bacterial biofilm presence and its potential impact on antibiotic treatment outcomes (8), but they are not typically employed for routine bacterial culture. Other methods, again not commonly used for routine diagnosis, include (19):

- Scanning electron microscopy
- Transmission electron microscopy
- Confocal laser scanning microscopy
- Fluorescent *in situ* hybridization
- Molecular biology, *e.g.*, polymerase chain reaction (PCR), which detects specific genes associated with the formation of biofilm

Given the challenges in directly visualizing biofilms, it is often necessary to use multiple methods in combination to achieve accurate and comprehensive identification.

Taming the biofilm: effective management strategies

As previously mentioned, biofilms confer bacteria with significantly increased resistance to antibiotics, often exhibiting 100-1,000 times greater resistance than planktonic bacteria (5). Consequently, it becomes imperative to develop strategic approaches to disrupt biofilms, thereby enabling antibiotic and antifungal treatments to effectively combat bacterial and fungal infections alike. The pursuit of innovative solutions to reduce biofilms not only enhances the efficacy of antibiotics, but also holds significant promise in addressing the challenges posed by antibiotic-resistant bacteria, and underscores the critical importance of ongoing research and development efforts in veterinary medicine. A review of some treatments that are commonly employed as adjuvant and have demonstrated effectiveness against biofilms is, therefore, worthwhile.

NAC (N-acetylcysteine) is a mucolytic agent that also possesses antimicrobial properties. While the exact mechanisms of its action on biofilms is only partially understood, it has been demonstrated to function as a biofilm-dissolving molecule. Specifically, it inhibits bacterial adhesion, decreases the production of extracellular polysaccharide matrix, and promotes the disruption of mature biofilms by breaking disulfide bonds within the extracellular matrix. This renders the biofilm more permeable and susceptible to antimicrobial treatments (20). Furthermore, its ability to destroy biofilms has been demonstrated *in vitro* with bacterial strains from the ear canal, namely *Staphylococcus pseudintermedius* and *Pseudomonas aeruginosa*. Its effectiveness varies depending on the concentration of NAC used, with approximately 1-2% recommended (13). Importantly, NAC has been proven safe during intratympanic injection in experimental conditions, making it a potentially non-ototoxic and viable option for treating chronically discharging ears (21).

Tris-EDTA (ethylenediaminetetraacetic acid-tromethamine) exerts its antimicrobial effects through a well-defined mechanism of action. The EDTA component functions as a chelating agent, sequestering divalent cations, which in turn disrupts the outer cell membrane of Gram-negative bacteria. This disruption leads to the release of lipopolysaccharides and renders the bacterial cells more permeable to other antimicrobial agents. Simultaneously, the Tris component acts as a buffer, enhancing the chelation capabilities of EDTA (22). While Tris-EDTA has demonstrated antibiofilm activity against *P. aeruginosa*, its effects on *Staphylococcus* spp. biofilms differ, often inhibiting their growth rather than eradicating them (13). It is worth noting that the combination of Tris-EDTA with certain antimicrobial agents might lead to a reduction in antibacterial efficacy, and further research is needed to fully understand these interactions. However, Tris-EDTA shines as an adjuvant in combination with some antimicrobial agents, where it exhibits synergistic antibiofilm activity. Studies have demonstrated that Tris-EDTA can reduce minimum bactericidal concentrations

"One of the key factors of bacterial biofilms is their ability to create a protective barrier that is resistant to antibiotics. Bacteria embedded in a biofilm are better protected against the effects of antimicrobial treatments, making biofilm-associated infections more challenging to eliminate."

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(MBCs) and minimum inhibitory concentrations (MICs), thereby enhancing the efficacy of antibiotics like marbofloxacin and gentamicin, especially in cases of multidrug-resistant *P. aeruginosa in vitro* (22).

In addition to Tris-EDTA, several other compounds have shown activity against biofilms, diversifying the arsenal of tools available in the battle against bacterial infections. For example, silver nanoparticles, povidone iodine and honey all provide alternatives for biofilm management (23,24). Moreover, ongoing research in the biofilm field continues to yield exciting discoveries. Innovations such as cold atmospheric microwave plasma, quorum sensing inhibitors and bacteriophages are emerging as potential agents with antibiofilm effects (23,25). These approaches hold the promise of enhancing our ability to combat biofilm-related challenges, offering hope for more effective treatment strategies in the future.

CONCLUSION

Biofilm formation represents an important virulence factor for various bacterial infections, including *Pseudomonas* spp. and *Staphylococcus* spp., especially in the context of chronic otitis. However, it is crucial not to neglect the role of yeasts such as *Malassezia* spp. in the role of biofilm production. When facing treatment failures characterized by specific macroscopic and microscopic features, considering the potential involvement of biofilm formation is paramount. Detecting and suspecting biofilm presence can lead to more adequate therapeutic strategies and increased hope of eradicating these stubborn infections.

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THE SKIN BARRIER IN CANINE ATOPIC DERMATITIS

Progress continues to be made on our understanding of canine atopic dermatitis; this paper looks in particular at the role of the skin barrier and how its dysfunction may contribute to the condition.

KEY POINTS

1. There is some evidence that a defective skin barrier is a key factor in a dog that develops atopic dermatitis (AD).
2. An individual dog's skin microbiota is thought to be another major aspect in determining if AD is likely to develop.
3. Various factors, including secondary bacterial and yeast infections, flea allergy and adverse food reactions, can make AD worse.
4. A multimodal approach to treatment is often essential to control AD long-term, including a focus on maintaining a healthy skin barrier.

Introduction

Skin is an amazing structure and the biggest organ of the body. It serves as a vital barrier between the internal organs and the external environment, protecting an individual from foreign substances and contributing to overall health, and the skin epidermis has evolved to become a dynamic structure with homeostatic capabilities that can cope with altering external conditions. This paper will review the role of the skin barrier in relation to canine atopic dermatitis (cAD) and discuss how best to optimize its health.

Epidermal anatomy

The epidermal layer of the skin consists of several tiers of corneocytes, namely (from inside to outside) the stratum basale, stratum spinosum, stratum granulosum, and stratum corneum (SC). The corneocyte is the final product of epidermal keratinization, and in dogs renewal of the epidermis takes about 22 days; new cells originating from the basal layer migrate upwards to replace the outer layer of dead cells. The cells are held together by a lipid matrix, comprising cholesterol, free fatty acids and ceramides which contribute to forming extracellular lipid-enriched lamellar membranes. A commonly used analogy to describe the skin barrier is the "brick wall theory" whereby the SC forms the "bricks", while the lipid-enriched layers between the cells forms the "mortar" **(Figure 1a)** (1). The integrity of the SC, particularly the lipid matrix, is important in maintaining the skin barrier function.

In addition to intercellular lipids, the outermost layer of the SC is coated with a variety of hydrophobic molecules, forming a protective barrier against microbes and allergens. Skin surface function and skin surface lipids have been investigated extensively in atopic dermatitis (AD) of both humans and dogs, and changes in lipid composition (free fatty acids and ceramides) in AD lesional skin and the lamellar conformation are thought to compromise the integrity of the skin barrier **(Figure 1b)** (2). Although definitive evidence of the relationship between skin barrier dysfunction and the development of cAD is still lacking, a few candidate genes have been associated with defective epidermal barrier integrity in cAD, such as those encoding for the exoskeleton protein plakophilin 2 (*PKP2*) and filaggrin (*FLG*) (3). In human medicine, transepidermal water loss (TEWL) and skin hydration (SH) are used to evaluate skin barrier function, treatment efficacy in atopy patients, and assessment of cosmetic products (4). TEWL and SH measurements are often included in clinical trials due to their noninvasive and convenient nature, but these techniques have not yet been standardized for use in dogs.

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Dr. Hsiao obtained her veterinary degree from Chia-yi University and went on to complete a Master's program in surgery at Chung-Hsing University in Taiwan before following a residency at the Asian College of Veterinary Dermatology (AiCVD) to gain her diploma. She then spent seven years at a dermatology referral center in Taipei, Taiwan before relocating to Japan in 2019 to become a member of the Vet Derm Tokyo dermatology group. Alongside her clinical practice, she is also involved in veterinary laboratory analysis tests.

Skin microbiota

Skin is also colonized by a diverse range of microorganisms (bacteria, *Malassezia* and fungi) known as the microbiota. In recent years, advances in next-generation sequencing have enabled identification of a wide range of cutaneous residents, and the microbiota can vary significantly between different body sites in the same dog. It is notable that it is susceptible to influences from factors such as topical therapy, systemic medications (especially antimicrobials), and even environmental conditions.

The exposure to a wide-spectrum microbiota during early life contributes to its adaptation to non-harmful microorganisms (5), and reflects the so-called "hygiene hypothesis" of human atopy. This was proposed in 1989 to explain the increasing prevalence of atopic conditions seen in humans; it suggests that a higher incidence of childhood infections might provide protection against the development of atopic diseases in later life. Babies tend to be born with an immune response that is Th (T-helper cell) 2 biased; this can be switched off rapidly postnatally under the influence of microbiological exposure, or can be enhanced by early exposure to allergens. Th2 cells are known to be involved with allergic responses, whereas the Th1 response is essentially mounted against infectious pathogens. Ideally, the two should be in equilibrium; a balanced Th1/Th2 pattern has been observed in infants that are less likely to develop atopic disease in later life. Unfortunately, there is no current research that supports the hygiene hypothesis in AD dogs, but research indicates a lower diversity in the skin microbiome in atopic dogs when compared to healthy dogs, which exhibit a rich diversity in their microbiota (6). Furthermore, when dogs with AD experience acute flares, there is a temporary disruption in the balance of their microbiota (dysbiosis) due to a substantial increase in *Staphylococcus* spp. However, after antimicrobial therapy and during remission of lesions, TEWL is reduced, and microbial diversity is restored (7).

Canine atopic dermatitis

cAD is a pruritic and predominantly T-cell driven inflammatory skin disease. Its development has a multifactorial pathogenesis, involving a complex interplay between immune dysregulation, skin

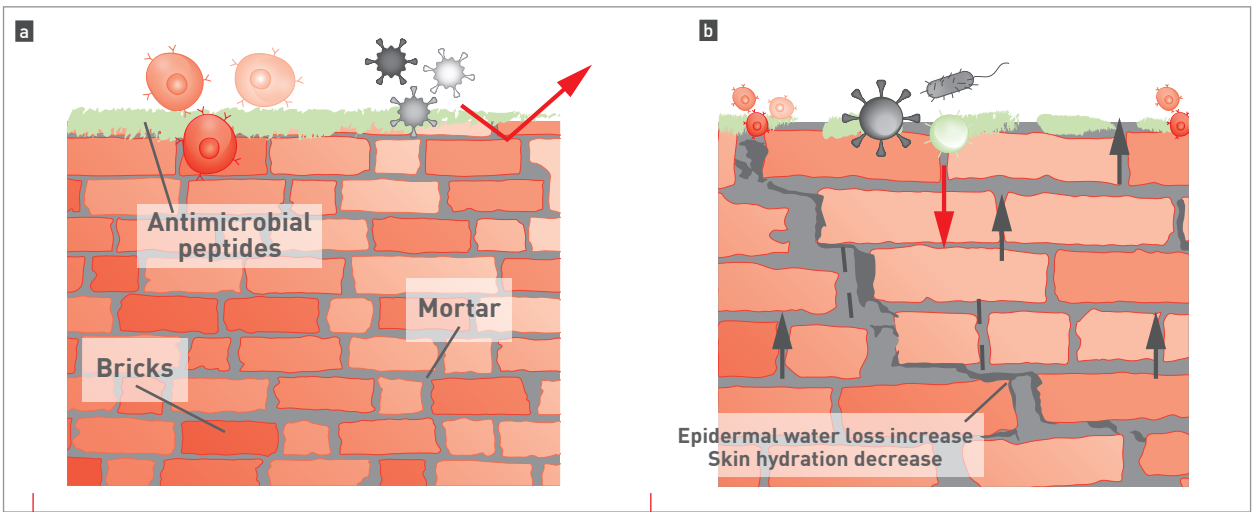

Figure 1a. The concept of the "brick and mortar" stratum corneum model involves solid building blocks (the cornified layers) held together by a space-filling mortar. Within the skin lipid matrix are peptides known for their antimicrobial properties, keeping the normal flora balanced and suppressing pathogenic bacteria.

Figure 1b. The "bricks and mortar" model lends itself to demonstrating what happens with a compromised epidermal barrier; this leads to reduced ceramide distribution, increased epidermal water loss, and decreased skin hydration. Note that skin lipid barrier defects may not effectively prevent the penetration of microbes and allergens.

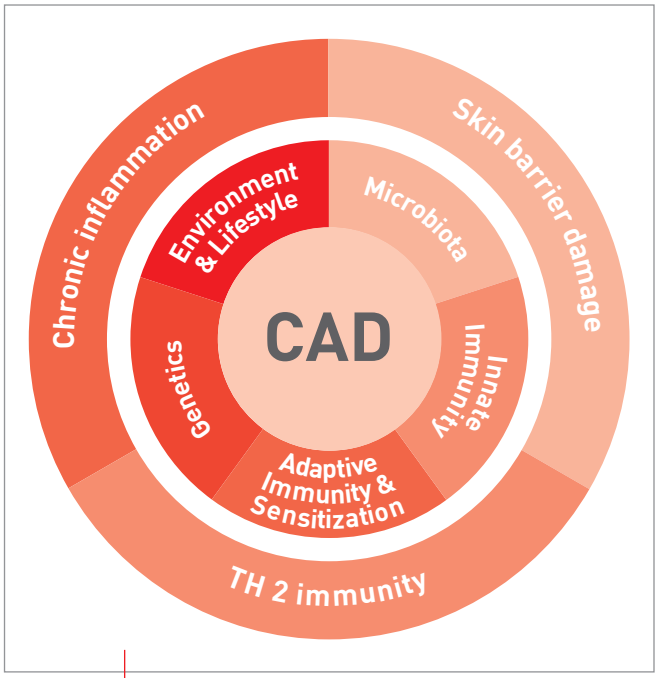

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Figure 2. There are various interacting factors in the pathogenesis of cAD; despite it being considered a single disease entity, it is imperative to employ diverse therapeutic strategies to manage it effectively.

barrier abnormalities, genetic predisposition, environmental factors and dysbiosis **(Figure 2)**. It is suggested that the environmental factors play a significant role in the development of cAD (3), as a dog's lifestyle, particularly during puppyhood, has a notable influence on maturation of the immune system. As such, growing up in a rural environment, having a large number of family members, and being in contact with other animals may lower the risk of developing cAD later in life. In addition, there is also an indication that *Toxocara canis* infection might have a protective effect against *Dermatophagoides farina* (house dust mite)-induced cAD (3).

The primary clinical feature of cAD is pruritus, which can present as either a seasonal or non-seasonal pattern. Lesions are commonly found in areas such as the periocular region, around the muzzle, axillae, inguinal region, perianal area, and the extremities **(Figure 3)**. Dogs with cAD may experience recurrent problems such as otitis externa and pododermatitis, which are commonly associated with secondary bacterial infections or an overgrowth of *Malassezia*. Diagnosing cAD relies on the exclusion of other pruritic skin conditions, especially those that mimic cAD, such as flea infestation/flea bite hypersensitivity, scabies, and adverse food reaction (AFR). Once ectoparasite prevention, diagnostic examinations and food trials have been successfully performed, Favrot's criteria can be used to establish a clinical diagnosis of cAD **(Table 1)** (8). For identification of cAD-related allergens, skin testing and IgE serology tests are available, although it should be realized that these tests are only needed if allergen-specific immunotherapy is considered (9).

Complicating factors – pyoderma

Staphylococcus pseudintermedius is one of the commensals on the canine skin and an opportunistic pathogen in pyoderma and otitis externa, commonly associated with underlying cAD

Table 1. Favrot's criteria for canine atopic dermatitis. If 5 or more of the criteria are met, there is at least an 80% chance that AD is the cause of the pruritus.

1.Onset of signs under 3 years of age
2.Dog living mostly indoors
3.Glucocorticoid-responsive pruritus
4.Pruritus without lesions (*sine materia*) at onset
5.Affected front feet
6.Affected ear pinnae
7.Non-affected ear margins
8.Non-affected dorsolumbar area

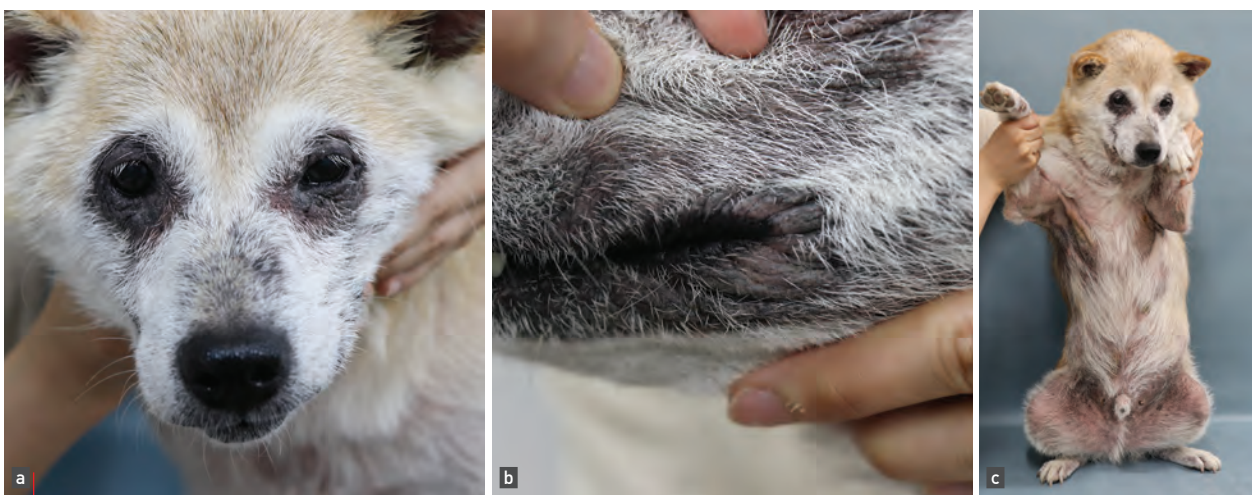

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Figure 3. The common distribution and clinical presentation of cAD; hair loss around the eyes **(a)**, muzzle **(b)** and ventrum **(c)**.

and/or adverse food reactions (10). Healthy skin has its own defense mechanisms to prevent bacterial overgrowth, such as antimicrobial peptides (AMP), beta-defensins (BDs), and cathelicidins (caths), located in the extracellular spaces of the SC (11). The microbiota and the skin barrier work together to maintain integrity and defend against the external environment. The precise factors contributing to increased susceptibility of dogs with AD to *Staphylococcus* spp. infections are not fully elucidated. The diagnosis of a bacterial skin infection (superficial folliculitis and pyoderma) is based on the clinical presentation (papules, pustules or epidermal collarettes - **Figure 4**) and the presence of intracellular cocci on cytology. Effective management of secondary bacterial infections can be accomplished through topical treatments. Maintaining skin and coat hygiene by shampooing can be particularly beneficial for dogs with cAD, as it helps promote a healthy skin barrier. Shampooing diminishes the allergens attached to the skin surface or hair coat, preventing further irritation. Moreover, *in-vitro* studies suggest that shampoo or mousse preparations that include antiseptic ingredients can have residual effectiveness for up to 14 days (12), so products containing chlorhexidine, benzoyl peroxide, ethyl lactate, povidone iodine or triclosan may be beneficial in treating superficial pyoderma (13). These should be used 2-3 times weekly, and then tapered down to once a week if the lesions resolve (13). In addition, mupirocin and fusidic acid are recommended as topical antimicrobial agents, due to the lower risk of developing multidrug-resistant *S. pseudintermedius* (MRSP). Systemic antimicrobial therapy should only be considered if topical treatment proves ineffective or if the infection's depth and location exceed the scope of topical therapy, with antibiotics selected on the basis of bacterial sensitivity tests. In general, the treatment course should be continued for 2 weeks after remission of the lesions. However, due to the global emergence of MRSP, it is highly advisable to prioritize topical treatments over repeated systemic antimicrobial therapy if the patient's condition allows.

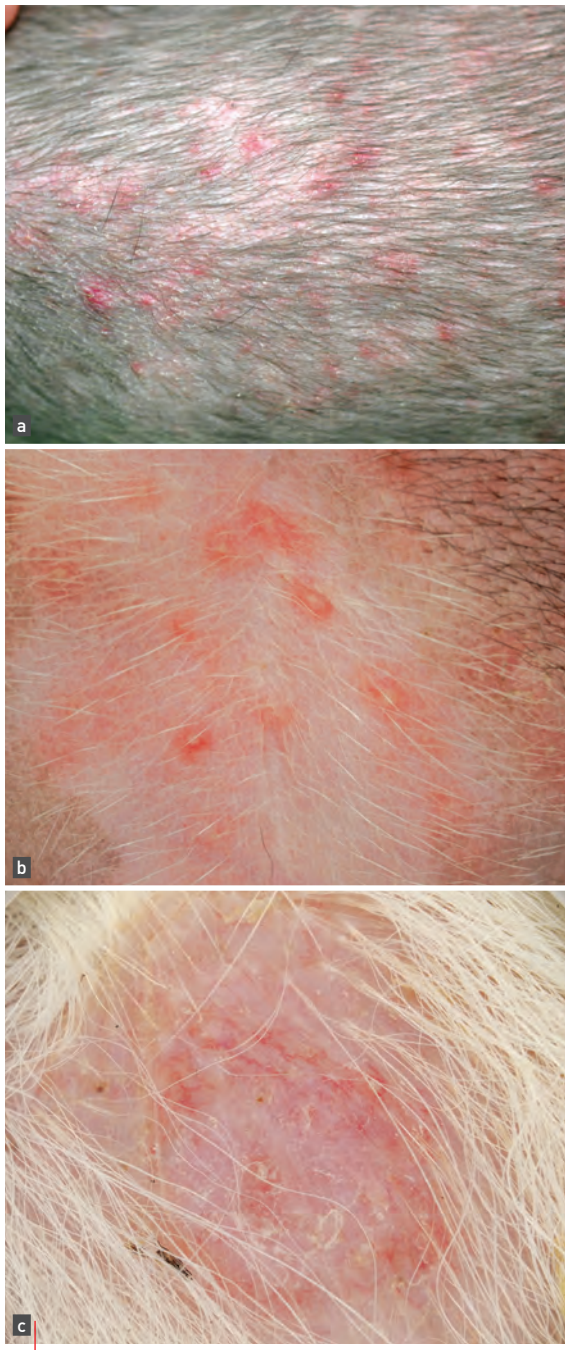

Figure 4. Papules **(a)**, pustules **(b)** and erythematous collarettes **(c)** are all common clinical signs of superficial bacterial infection secondary to atopic dermatitis.

Complicating factors – *Malassezia*

Malassezia pachydermatis is a lipid-dependent yeast found on the skin surface. Excessive surface lipids, disruptions in the SC barrier function, and an aberrant immune reaction in cAD may contribute to overgrowth of this opportunistic pathogen (14). Colonization in puppies occurs in a similar fashion to that of *Staphylococcus* spp., with transmission through licking and nursing by the mother at the very early stages of life. When the conditions are favorable, *Malassezia* can proliferate within the SC, producing numerous antigens and allergens (14). These antigens can penetrate the epidermis and trigger an immune response in cAD dogs, resulting in pruritus and erythema. *Malassezia* tends to flourish in areas of the skin with high humidity, such as skin folds around the ears, lips, anus, axillae, inguinal region and the claws/interdigital areas. Clinical presentations may manifest as pruritus and erythema, accompanied by malodor or a greasy skin coat. There is no gold standard for diagnosing *Malassezia* dermatitis, but skin cytology and a compatible clinical presentation are the most effective methods; culture, histopathology and IgE tests lack substantial clinical diagnostic value.

The primary treatment options consist of antifungal agents such as topical imidazoles, clotrimazole, climbazole, and miconazole. Terbinafine and 2% chlorhexidine/2% miconazole shampoo are

alternatives. However, although antiseptic ingredients can substantially diminish a *Malassezia* overgrowth, emollient bathing products containing cleansing oils, and emollient shampoos with a ceramide-based moisturizer have also demonstrated similar clinical efficacy (15).

Complicating factors – fleas and adverse food reactions

Flea control and elimination of food allergens are vital strategies in managing cAD, as these help lower the threshold for pruritus, ultimately improving the patient's quality of life. Oral adulticides are indicated for efficient year-round control of fleas, as shampooing can flush out topical products and reduce their effectiveness. Isoxazoline products have demonstrated a rapid onset of efficacy, being able to eliminate fleas within 24 hours of administration, which prevents further flea bites.

Adverse food reactions can coexist with cAD, with estimates ranging from 9-50% among dogs displaying lesions indicative of cAD. To differentiate AFR and atopic dermatitis (which is mainly due to environmental allergens) a strict 8-week food trial based on a novel or hydrolyzed protein diet must be followed. It is also advisable to consider provocative testing after the food trial in order to identify specific food allergens and subsequently remove them from the dog's daily diet. Although the exact immune mechanism of AFR is not fully understood, a study in affected dogs that had shown significant clinical improvement on an elimination diet trial reported that 90% went on to display clinical signs again (pruritus, feet licking, face rubbing) when tested subsequently, some within a few hours of being fed the provocative diet (16).

Control and management of cAD

cAD is a skin disease which cannot be cured, and it usually requires life-long management customized for the individual patient. Allergen-specific immunotherapy (ASIT) is considered the specific treatment, involving injections of increasing concentrations of environmental allergens identified by skin testing and IgE serology. The clinical effectiveness of ASIT is approximately 60% and may require 9-12 months treatment before noticeable improvement (17). Recently, intralymphatic and sublingual immunotherapy options have been introduced as alternatives to the traditional subcutaneous injection method; these offer a more rapid induction, and the former method is needle-free (18). However, it is essential to manage the pruritus and skin lesions continuously until clinical signs are alleviated through ASIT. Management of cAD depends on the stage of the disease – so for example, rapid intervention with acute flares, control of the chronic disease, or prevention of relapses. As pruritus is the key sign of AD and skin lesions are common secondary to this, treatment should be focused on diminishing the itch. Depending on the intensity of the pruritus, and the distribution and extent of the lesions, topical and/or systemic medication can be chosen. To control acute flares glucocorticoids (topical and systemic) and oclacitinib are considered to be the most effective because of their rapid action, although glucocorticoids are noted for potential adverse effects, which may include polyuria, polydipsia, polyphagia, increased susceptibility to infections, and iatrogenic hyperadrenocorticism. Long-term or high-dose use of glucocorticoids should be carefully monitored, with a switch to other regimes if possible. When the skin lesions have reduced to a mild level, oclacitinib is preferred for its effectiveness in managing residual pruritus and mild flares, as it diminishes the pruritogenic signaling pathway and pro-inflammatory cytokines. However, after the initial two-week twice-daily initiation phase, patients will often show a rebound phenomenon when tapered to once daily treatment (19). In order to prevent this, topical hydrocortisone aceponate can be added as combination therapy (20).

These regimes can be considered as reactive therapy, primarily to be used during ongoing flares or for pruritus management. Once the skin condition is under control, the treatment should be shifted, using narrow-target drugs which are less impactful to the individual, typically cyclosporine and tacrolimus. Cyclosporine is a calcinurin inhibitor which binds to lymphocyte cytoplasm, inhibiting activation of T cells and its down-regulation mediators. Nevertheless, the introduction of cyclosporine takes 2-4 weeks for clinical efficacy, but because of its prolonged half-life, patients have a better chance of tapering down to a lower frequency compared to other medications. It is considered safe for long-term administration, although patients may suffer from initial transient adverse effects such as vomiting

"It is suggested that environmental factors play a significant role in the development of cAD. A dog's lifestyle, particularly during puppyhood, has a notable influence on the maturation of the immune system."

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and diarrhea; these usually resolve spontaneously without further treatment. Tacrolimus ointment does not cause the adverse reactions (*e.g.*, skin atrophy or comedones) that are observed with topic glucocorticoids, but mild irritation might be noticed in some dogs. In well-managed cases, lokivetmab (a monoclonal antibody that targets interleukin (IL)-31, a common pruritus mediator in patients with cAD) is recommended as proactive therapy (21). The concept is to consistently diminish the residual subclinical inflammation that could potentially trigger sudden flares.

To prevent recurrence of cAD, direct restoration of the skin barrier function is another important factor, and oral essential fatty acid (EFAs) or fatty acid-enriched diets have been used for many years. EFAs have been demonstrated to reduce the medication score and pruritus in AD dogs over a 9-month duration (22), but antihistamines and probiotics have exhibited insufficient evidence to support their use as treatment options for cAD.

CONCLUSION

Canine atopic dermatitis (cAD) is a chronic relapsing pruritic skin disease that is commonly seen in veterinary practice. The pathogenesis is linked to the disruption of the skin barrier; genes associated with a defective stratum corneum, the microbiota and environmental factors influencing immune balance are all connected to its development. Treatment regimens and strategies have undergone significant progress over the past decade, but a proper diagnosis is the first step in managing the cAD patient. Concurrent bacterial and/or yeast infection may compromise treatment efficacy, and ultimately the choice of therapy depends on the phase and severity of the condition. Although atopic dermatitis is not curable, a multimodal approach can give the dog a good quality of life, and ensuring a healthy skin barrier should help prevent further exacerbations of pruritus and inflammation.

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HOW I APPROACH... FELINE ATOPIC SKIN SYNDROME

Cats will often present with dermatological signs that could be triggered by a plethora of different causes; here Sandra Diaz describes her approach to such cases.

KEY POINTS

1. The term Feline Atopic Skin Syndrome, or FASS, is now employed for allergic skin conditions in cats that are triggered by environmental allergens.
2. There are a limited number of common reaction patterns seen with feline dermatological problems, but the underlying cause can be difficult to identify.
3. Flea allergy is by far the most common feline skin condition.
4. Oclacitinib, maropitant and cannabinoids are all alternative treatment options that have been trialed in pruritic cats.

Introduction

Feline dermatology has advanced in the last few years with regard to disease recognition, better understanding of pathogenesis of existing diseases, and new treatment options. Furthermore, the terminology for feline allergic skin disease has been recently updated, and the term Feline Atopic Skin Syndrome, or FASS, is now employed in reference to allergic skin disease triggered by environmental allergens. FASS is challenging to diagnose, since various allergic skin diseases can present clinically with one or a combination of the following reaction patterns:

- miliary dermatitis,
- self-induced alopecia,
- eosinophilic granuloma complex,
- head and neck pruritus.

The skin reacts in these "patterns" to different underlying causes, but they look clinically identical. These reaction patterns can even be similar on histopathology, which may make the diagnosis very complex, causing frustration to both the cat's owner and the clinician. Because dermatitis due to fleas or adverse food reactions can also present with these cutaneous patterns it is crucial to rule them out when diagnosing FASS. In addition, other pruritic skin conditions, including parasitic (*Demodex gatoi, Otodectes cynotis, Notoedres cati, Cheyletiella blakei*), infectious (*Malassezia* dermatitis, superficial pyoderma, dermatophytosis), and autoimmune skin diseases (pemphigus foliaceus) need to be evaluated and ruled out or treated.

Miliary dermatitis

Miliary dermatitis, or papulocrustous dermatitis, is characterized clinically by numerous, small, localized or generalized erythematous and crusted papules **(Figure 1)**. It is the most common feline presentation in small animal dermatology, and the lesions can often be detected on palpation of the skin, especially in long-haired cats. The presence, extent and severity of pruritus, presence of skin lesions in animals or people in contact with the patient, seasonality, and response to previous medications are helpful when developing a list of differential diagnoses.

Self-inflicted alopecia

This can be caused by a variety of conditions; hypersensitivity dermatitis is often involved, although very rarely psychogenic problems can lead to self-inflicted alopecia **(Figure 2)**. Nevertheless, a combination of behavioral and allergic factors is

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frequently seen, particularly in overanxious breeds such as Siamese or Abyssinians. Hair loss can also be associated with telogen effluvium or hormonal disease such as hyperthyroidism or other internal problems. Infectious and parasitic diseases should also be considered, as mentioned previously. If the pet owner does not observe excessive grooming, a trichogram can be performed to evaluate the tips of the hair shafts; if these are broken, the alopecia is likely self-inflicted. Skin cytology, skin scrapings, direct examination of the hair, Wood's lamp examination and fungal cultures should be performed to rule in/out the possible differential diagnosis.

Eosinophilic granuloma complex

This consists of eosinophilic plaques or granulomas and/or indolent ulcers. Indolent ulcers appear as a unilateral or bilateral erosive to ulcerated lesions of the upper lip **(Figure 3)**. The well-circumscribed ulcers with raised borders are rarely painful or pruritic and do not cause major discomfort to the cat. The differential diagnoses are neoplastic diseases (such as squamous cell carcinoma) and infectious ulcers. Diagnosis is confirmed by biopsy, with prior antimicrobial treatment recommended if cytology is indicative of infection. Eosinophilic plaques are raised, erythematous, exudative and severely pruritic lesions that occur typically on the ventral abdomen or medial and caudal aspect of the thighs, and less frequently on the face and neck. Eosinophilic granulomas are non-pruritic, raised, firm, yellowish, linear to nodular lesions that occur most commonly on the caudal thighs (linear), oral cavity, interdigital spaces and chin (nodular).

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Figure 2. Self-inflicted alopecia in cats can be caused by a variety of conditions, but cats can be secretive, and pet owners may not observe excessive grooming; a trichogram can be performed to look for broken tips of the hair shafts if necessary.

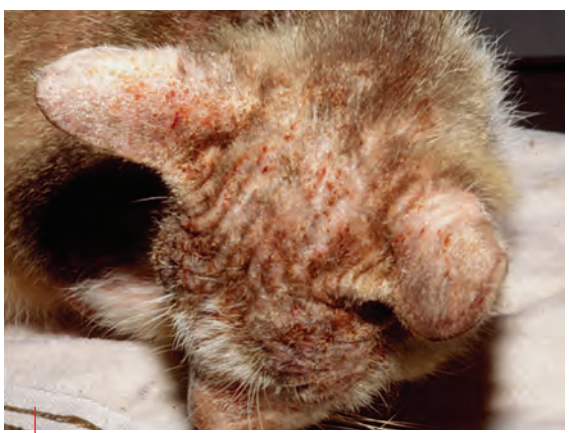

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Figure 1. Miliary dermatitis is the most common feline dermatological presentation, and is characterized clinically by numerous, small, localized or generalized erythematous and crusted papules.

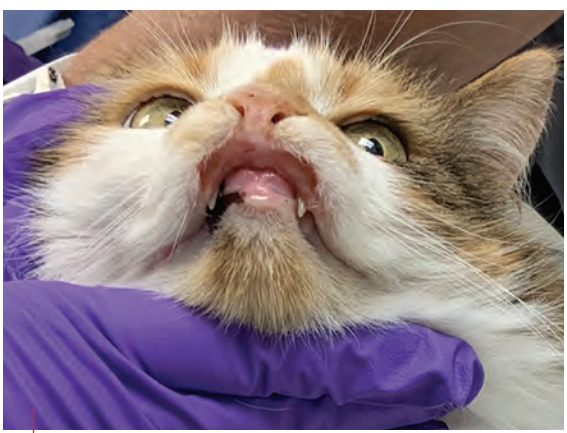

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Figure 3. Indolent ulcers are part of the eosiniphilic granuloma complex in cats; they most typically appear as unilateral or bilateral erosive to ulcerated lesions on the upper lips.

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Figure 4. Head and neck pruritus in the cat is often associated with significant self-trauma, alopecia, erosions, crusts and ulceration, and the eroded or ulcerated lesions are often secondarily infected.

Differential diagnoses of both eosinophilic plaques and granulomas include neoplastic, bacterial and fungal etiologies.

Diagnostic tests include skin cytology and biopsy, and once the diagnosis has been confirmed, the underlying cause needs to be identified and treated. If infectious and neoplastic causes have been ruled out, an allergic etiology is more likely.

Head and neck pruritus

Head and neck pruritus in the cat is often associated with significant self-trauma, alopecia, erosions, crusts and ulceration **(Figure 4)**. Differential diagnoses include allergies, as well as ectoparasites and infectious (bacterial, fungal, viral) dermatoses. Often the eroded or ulcerated lesions are secondarily infected with bacteria or yeast organisms, which need to be identified by cytology and treated appropriately. An elimination diet trial, ectoparasite treatment trial and flea control are important parts of the work-up. If no improvement is seen, biopsy and PCR testing for viral diseases (*e.g.*, herpesvirus) may be considered.

Flea allergy and differentials

Since flea allergy dermatitis is the most common type of allergic dermatitis in the cat, if pruritus is present, this is the first condition I like to rule out. Pruritus is variable, but it can be severe, resulting in severe excoriations and secondary pyoderma. There are a variety of flea products now on the market, and some of these which contain isoxazolines are not only effective for flea infestations, but other ectoparasites as well, including otodectes, notoedres, demodex and cheyletiella mites. These are generally spot-on preparations, but an oral medication containing lotilaner is also available. It is worth noting that the US FDA has released a fact sheet for pet owners and veterinarians about isoxazolines and their potential adverse events, which states "isoxazoline products have been associated with neurologic adverse reactions, including muscle tremors, ataxia, and seizures in some dogs and cats". When performing a treatment trial for parasitic skin diseases, ideally all animals in the household should be treated simultaneously. Environmental flea control can be recommended if considered necessary (*e.g.*, multiple pet households or densely populated pet areas); insect growth regulators such as methoprene or pyriproxifen can be safe and effective options for environmental control.

Although *D. gatoi* is not a common diagnosis, it is also important to be considered as a differential, and lime sulfur dips performed for at least six weeks can be effective if the mite is identified. Recently, treatment with a commercial spot-on preparation containing 10% imidacloprid/1% moxidectin at the manufacturer-recommended dose per body weight applied once a week (off label) has been reported to be effective (1), with resolution of the clinical signs after eight weeks of treatment. In this report, two additional treatments were recommended after resolution of the clinical signs. Fluralaner has also recently been reported as effective for the treatment of *D. gatoi* in two affected cats, with the animals receiving the oral chews available for dogs at a dose of 26-34 mg/kg (2). However, fluralaner is now available as a topical solution approved for use in cats in many countries.

If the pruritus is severe, a short course of oral glucocorticoids can be used to break the itch-scratch cycle. Prednisolone/prednisone is a good initial choice; I usually start with approximately 1 mg/kg every 24 hours for 3 to 5 days, then every 48 hours for 3 to 5 days, and then discontinue it.

I usually schedule a recheck appointment for four weeks; at that point, cats with flea allergy will be significantly improved.

Further diagnostics

Skin cytology to evaluate for the presence of secondary infections is also indicated at the initial evaluation. The findings will also help in the diagnosis of pemphigus foliaceus (PF) **(Figure 5)**, as the presence of significant number of acantholytic keratinocytes will raise suspicion of the condition; ruling out infectious causes, along with histopathology findings, will help confirm a diagnosis of PF. Dermatophytosis can also present as miliary dermatitis, and its diagnosis is based on Wood's lamp examination, direct examination of the hair, and fungal culture. Importantly, since dermatophytosis can clinically mimic so many other skin diseases, it should be considered and ruled out in all cats presenting with dermatologic disease.

Dermatitis due to adverse food reactions is also a very important differential diagnosis for a cat presenting with any of the above-mentioned cutaneous reaction patterns. Currently, the most

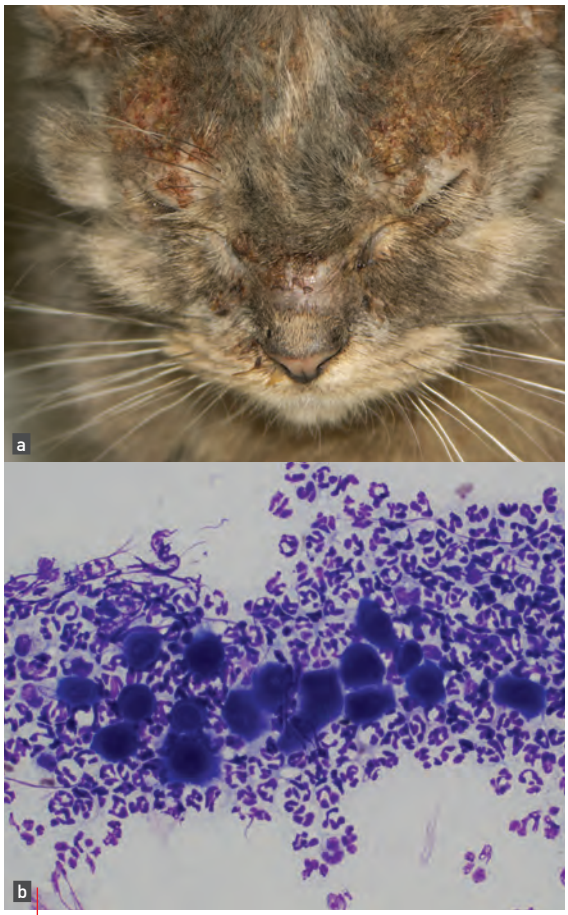

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Figure 5. Pemphigus foliaceus can cause severe head and neck lesions in affected cats **(a)**. The presence of significant numbers of acantholytic keratinocytes on skin cytology will raise suspicion of the condition, although they are not pathognomic **(b)**.

accurate way to diagnose or rule out an adverse food reaction, including food allergies, is performing a food elimination trial. Such a trial is very simple in concept, but usually difficult to implement, especially for cat owners. Food options include limited ingredient diets (commercial or homemade) and hydrolyzed protein diets. Note, however, that most hydrolyzed diets currently available have proteins of molecular weight between 6-12 kD, except for one commercial diet, which is ⩽ 1 kD[1]. I personally prefer a limited ingredient diet (chosen based on previous dietary history) or Ultamino, but eventually the cat will determine "the ideal diet" based on what they decide to eat. The selected food should be fed exclusively for a minimum of 8 weeks; a recent evidence-based analysis concluded that for diagnosing adverse food reactions in more than 90% of dogs and cats, elimination diet trials should last for at least this period (3). At the end of 8 weeks, if the clinical signs have improved, the cat should be "challenged" with the original diet (for up to 2 weeks) and observed for recurrence or worsening of the clinical signs. If the clinical signs recur, and then resolve with the re-introduction of the diet used during the trial, this then confirms a diagnosis of adverse food reaction. Dedicated pet owners may choose to perform a "sequential challenge" to identify the offending protein, whereby one new protein is added to the diet every two weeks. Once the offending protein is identified, it must be avoided in the future. If using a home-cooked diet, seek advice from a veterinary nutritionist for long-term use to assure that the diet is balanced.

If none of these diagnostic tests/trials has led to a definitive diagnosis, then hypersensitivity to environmental allergens is the more likely diagnosis. At this point, the client has the choice of either pursuing symptomatic therapy, and/or allergen-specific immunotherapy (ASIT).

Therapy for FASS

Allergen-specific immunotherapy

To formulate ASIT, the offending allergens need to be identified, and allergy testing is recommended (via skin and/or serum allergy testing) if the clients choose to manage their cats with this option. Approximately 60-75% of patients have a good to excellent response to ASIT, but it may take up to a year before a clinical response is seen, and adjunctive symptomatic therapy is often needed during the first 6-12 months of treatment. Once ASIT successfully controls the clinical signs, other therapies can be tapered and often discontinued. Premature treatment discontinuation is a relatively common cause of treatment failure, and in our practice a year's supply of ASIT is dispensed, making early discontinuation less likely.

Whilst ASIT is a relatively safe and well-tolerated treatment for cats diagnosed with FASS, client education and routine follow ups are essential for treatment success; allergy companies are a good resource for client education brochures and technical assistance. The clinic's veterinary technicians can also provide excellent support to clients during their pet's treatment. Referral to a veterinary dermatologist for testing and ASIT implementation is always a good option.

Symptomatic therapy

Most commonly used symptomatic therapies include fatty acids, antihistamines, glucocorticoids, and cyclosporine. Fatty acid supplementation and antihistamines have a success rate of approximately 25%, although given together they have a synergistic effect which may increase the success rate. Chlorpheniramine (2-4 mg PO per cat q12h), hydroxyzine (10 mg PO per cat q12h); clemastine (0.68 mg PO per cat q12h) are the antihistamines I use more commonly. Amitriptyline is a tricyclic antidepressant, with antihistaminic, anti-inflammatory and sedative actions, which can be given orally or intradermally; the latter may be beneficial for cat/pet owners who have difficulty

[1] Ultamino/Anallergenic (Royal Canin)

medicating their cats. I start amitriptyline at 10 mg per cat q24h. Although not common, adverse effects to antihistamines in cats include sedation, hypersalivation, urinary retention, anorexia, vomiting/nausea and dysrhythmias, so it is important to evaluate for any pre-existing problem that may increase the risk of developing these side effects and monitor during treatment. Pre-treatment bloodwork and urinalysis and monitoring every 6 months is recommended.

Glucocorticoids are used frequently in various formulations, and glucocorticoid-induced adverse effects are less common in cats than in dogs, although marked and unique problems may occur. Several studies have documented cardiovascular risks associated with glucocorticoid use in cats; for example, an association between long-acting depot corticosteroids (*e.g.*, methylprednisolone acetate) and the development of congestive heart failure in cats without pre-existing cardiac disease has been seen (4). Diabetes is also a relatively common side effect; in one study, up to 75% of cats showed hyperglycemia after a single 5 mg/kg subcutaneous injection of methylprednisolone acetate (5). Diabetes may be transient or permanent after discontinuation of therapy.

Prednisolone or methylprednisolone can be started at 0.5-1 mg/kg PO q24h for 5-7 days, then on alternate days at the lower effective dose. If the cat cannot be well-controlled with ⩽ 0.5 mg/kg q48 h or less, alternative therapies may need to be evaluated. If prednisolone is not effective, triamcinolone or dexamethasone can be tried. Triamcinolone can be started at 0.2 mg/kg PO q24 for 5-7 days, then tapered to lowest effective dose, ideally ⩽ 0.08 mg/kg q48-72h. Dexamethasone is started at 0.25-1 mg per cat PO q24h for 5-7 days, then tapered to lowest effective dose, ideally ⩽ 0.125 mg q48-72h. Complete blood count (CBC), chemistry profile and urinalysis are recommended to be performed at baseline and every 6-12 months in cats receiving maintenance glucocorticoid dosing.

For long-term control of pruritus in a cat with FASS, I prefer cyclosporine (CsA); studies have shown it to be an effective and safe treatment option (6), and I usually start at 5-7 mg/kg every 24h; a recent study suggested 7 mg/kg as the optimal dose (7). Initial improvement can be seen by the second week of treatment, but it may take 4-6 weeks for a full response. Treatment is usually well-tolerated; vomiting and/or diarrhea may occur, but in most cases signs resolve without discontinuation of treatment. Although a rare complication, fatal toxoplasmosis has been reported (8). It is recommended to exclude seronegative outdoor cats from treatment; cats seropositive to *Toxoplasma* seem to be protected from acute fatal disease. The decision to treat seropositive cats should consider possible relapses, and potential complications need to be discussed with the client. The same survey tests (at the same interval) recommended for cats on glucocorticoids are also recommended for those receiving maintenance CsA therapy.

"If the owner does not observe excessive grooming, a trichogram can be performed to evaluate the tips of the hair shafts; if these are broken, the alopecia is likely self-inflicted."

Sandra Diaz

Other treatment options

Oclacitinib, a Janus kinase inhibitor, has been used off-label for the treatment of FASS. Pharmacokinetic studies showed that this drug is absorbed and eliminated faster in cats than in dogs (9), therefore a shorter dosing interval and higher dose may be needed in cats. A safety study performed in healthy cats given 1 or 2 mg/kg q12h for 28 days reported vomiting and soft stools in the cats given 2 mg/kg (10). In a methylprednisolone-controlled study, oclacitinib given at 0.7-1.2 mg/kg q12h was as effective as methylprednisolone controlling the clinical signs of FASS (11). No long-term safety studies have been performed in cats receiving oclacitinib, so this and its off-label use should be discussed with clients before initiating treatment. Reported side effects include anemia, vomiting, and an increase in ALT, creatinine, BUN, and soft stools in *Giardia*-positive individuals (9). There is one report of acute fatal toxoplasmosis in a cat receiving oclacitinib (12).

Maropitant is a neurokinin-1 receptor antagonist (NK-1 R), which inhibits the action of substance P. Substance P activates receptors in mast cells and sensory neurons, causing itch. Maropitant has been used orally at 2.2 mg/kg q24h for the control of FASS in an open study (13), with owners reporting good to excellent response in 83.3% of the cases after a 4-week course. Oral maropitant citrate is not labeled for use in cats in the United States, and no long-term safety studies have been performed in cats receiving this drug, so again this and its off-label use should be discussed with clients before initiating treatment. A recent clinical trial indicated that transdermal application of maropitant in cats experiencing vomiting may be a good and effective alternative; however, further studies are needed to determine dosing and pharmacokinetics (14).

Cannabinoids are biologically active substances similar to the primary psychoactive compound found in *Cannabis sativa*. They can be plant-derived, synthetic, or endogenous (endocannabinoids).

Endocannabinoids are naturally produced by the body and include arachidonoylethanolamide (AEA), 2-arachidonoylglycerol (2-AG), and N-palmitoylethanolamide (PEA). Endocannabinoids bind to cannabinoid (CB)1 and 2 receptors. The activation of CB2 receptors on mast cells decreases the release of inflammatory cytokines such as IL-2, and upregulates IL-10, an anti-inflammatory cytokine. Cannabinoid receptors can also be found in skin sensory nerve fibers, and activation of these receptors may reduce the sensation of pruritus. A recent study showed increased expression of CB1 and CB2 in cats with allergies when compared to healthy cats, suggesting that the use of cannabinoid receptor agonists like PEA may be useful in the treatment of FASS (15). Some countries now have a licensed cannabinoid available; for example, one product now marketed in the USA is a powdered, flavorless and odorless supplement, containing 60 mg of PEA per 2 mL scoop; the recommended dose is one scoop/day in cats up to 4 kg (9 lb) and 1½ scoops/day in cats weighting more than 4 kg. This product can be sprinkled on food and is well-tolerated with minimal side effects.

Gabapentin is a neuroactive agent used to treat neuropathic pain. Chronic pruritus causes neuronal sensitization, with hypersensitivity of sensory neurons to itch stimuli. Gabapentinoids such as gabapentin and pregabalin have been used for neuropathic forms of chronic pruritus in people with good response. Gabapentin has been used in cats for treatment of feline hyperesthesia syndrome, either as sole therapy or in combination with other anti-pruritic therapy (16). I start this treatment at 10 mg/kg PO every 12 hours, often in combination with PEA, or as a glucocorticoid-sparing treatment. Reported side effects, although uncommon, include sedation, ataxia, weakness and muscle tremors.

CONCLUSION

Since feline dermatological conditions tend to present with a relatively few classic patterns, the differential diagnosis can be problematic. A rigorous systematic approach, coupled with a few simple diagnostic tests, can often identify the more common causes. Treatment options are varied and will depend ultimately on the etiology, but good flea control and a sensible anti-pruritic regime can often help cats with a skin allergy to enjoy a good quality of life.

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