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SCIENTIFIC RESEARCH AND VETERINARY INFORMATION

A balanced microbiome for healthy skin

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ICF Evolution of Knowledge

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An important aspect to consider for our pets' health and well-being is the balance of their skin microbiome. The skin microbiome is made up of a wide range of bacteria, fungi, and other micro-organisms that colonise the surface and play a key role in the health of the skin and the entire body. An imbalance in the skin microbiome can be an indicator, as well as a root cause of a variety of dermatological and general health issues.

The importance of the skin microbiome

The skin microbiome creates a true **microbiological barrier** that works in conjunction with the mechanical and immunological barriers to prevent infection and regulate the immune system. First, occupying ecological niches on the surface of the skin, it avoids proliferation of pathogenic harmful microorganisms, acting as a true protective barrier against bacterial and fungal infections. Second, through the action of enzymes produced by bacteria, the skin microbiome contributes to the production of lipids and other components that help keep the skin hydrated and protected by enriching the superficial lipid film. Lastly, the skin microbiome interacts with the skin immune system, including keratinocytes, directing it to regulate its response to allergens and to pathogenic micro-organisms (Belkaid and Segre, 2014; Grice et al., 2011).

Keratinocytes sample the micro-organisms colonising the skin surface through pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), mannose receptors, and NOD-like receptors. These receptors recognise pathogen-associated molecular patterns (PAMPs), i.e. structures belonging to micro-organisms, such as flagellin and nucleic acids, as well as lipopolysaccharides from Gram-negative bacteria, mannan and zymosin from fungi, and peptidoglycan and lipoteichoic acid from Gram-positive bacteria. The activation of keratinocyte receptors by PAMPs initiates the innate immune response, resulting in the secretion of antimicrobial peptides (AMPs), cytokines and chemokines. Beyond activating an adaptive immune response, AMPs also directly kill bacteria, fungi and viruses with envelope.

It is important to underline that the skin's immune system can discriminate between harmless commensal micro-organisms and harmful pathogenic micro-organisms, maybe because the TLRs may be desensitised by prolonged exposure to commensal micro-organisms. Also, *Staphylococcus epidermis* and *Propionibacterium*, commensal bacteria, can stimulate the host's innate immune response to produce cytokines and antimicrobial peptides and improve the elimination of pathogenic bacteria (Lai et al, 2010; Nagy et al., 2,005).

Composition of the skin microbiome in humans and dogs

Every square centimetre of human skin is covered with 1,000 to 1 million micro-organisms. More than 1,200 bacterial species are recognised to live on human skin, with the genera *Propionibacterium, Staphylococcus* and *Corynebacterium predominating*.

The bacterial and fungal taxa of canine skin differ from those of human skin. Dog skin is dominated by *Proteobacteria*, *Firmicutes*, *Fusobacteria*, *Bacteroides* and *Actinobacteria*, and environmental fungi such as *Alternaria* and *Cladosporium*. In contrast, human skin is colonised more abundantly by bacteria of the phyla *Actinobacteria* and *Firmicutes* and the fungal genus *Malassezia* (Rodrigues-Hoffmann et al., 2014).

Imbalances in the skin microbiome (dysbiosis)

Numerous factors can upset the skin microbiome's balance, and when this happens, several issues can develop. The most frequent cause of skin dysbiosis in dogs is undoubtedly **allergic dermatitis** (Fig. 1), in which changes in the normal bacterial and fungal microbiota have been identified (Rodrigues-Hoffman et al., 2014; Santoro et al., 2015). As in humans, the skin of allergic dogs shows a reduced diversity of bacterial microbiota: the number of bacterial species reported from allergic skin is significantly lower than the same sites on healthy dogs. Dogs with acute forms of atopic dermatitis have significantly higher proportions of *Staphylococcus spp* (*S. pseudintermedius* in particular) and *Corynebacterium spp* at all skin sites compared to healthy control dogs. The positive correlation between the relative abundance of *Staphylococcus* and the severity of the lesions suggests that the amount of *Staphylococcus* increases with disease severity. *Staphylococcus* overpopulation at the cost of other species predisposes to pyoderma and hinders the immune system's proper function.

Atopic dermatitis lesions in humans show low levels of AMP production compared with healthy skin. In addition, some pathogenic bacteria produce toxins (Salava and Lauerma, 2014) that cause inflammation and dysfunction of the skin barrier through activation of the host's innate immune system, leading to disease flare-ups and the development of skin lesions.

Figure 1: Allergic patient with signs of skin dysbiosis (copyright Dr C. Noli).

Other causes of dysbiosis may be conditions that lead to **reduced immune responses**, including endocrinopathies, serious systemic diseases, and the use of immunosuppressive drugs.

It is not unusual for the skin's immune barrier to be compromised in these circumstances, allowing the growth of opportunistic pathogens like *Staphylococcus pseudintermedius* and *Malassezia pachydermatis*, leading to the onset of pyoderma (Fig. 2) and/or yeast dermatitis (Fig. 3).

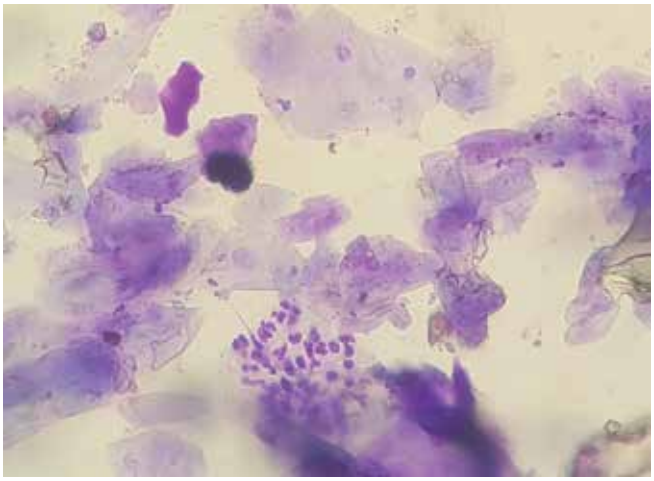


Figure 2: Cytological examination using the scotch test method showing the presence of corneocytes and neutrophil granulocytes with some coccus bacteria

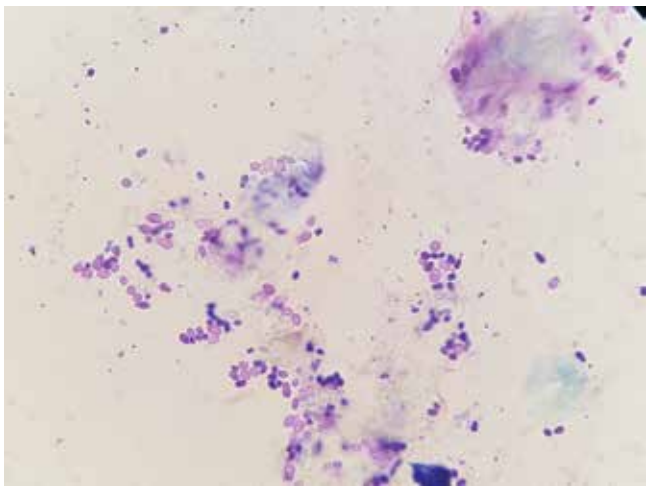


Figure 3: Cytological examination using the scotch test method showing the presence of Malassezia yeasts.

A **microbial barrier disorder** may contribute to skin dysbiosis. For instance, overusing shampoos and other skin care products—especially those with aggressive formulas that might change the pH of the skin—when it is not necessary can upset the balance of the surface microbiome. Excessive use of antibiotics, especially if systemic, alters the normal skin and enteric microbiome, often allowing resistant pathogenic bacteria to proliferate.

Finally, a disorder of the **mechanical barrier** can also promote the colonisation of opportunistic micro-organisms and the development of infections (Fig.4). Examples of these conditions include metabolic diseases (metabolic necrosis of the epidermis, zinc-responsive dermatitis), congenital keratinisation disorders (idiopathic seborrhea, ichthyosis), and some autoimmune diseases characterised by dysepithelialisation (lupus, vesicular diseases of the dermo-epidermal junction, toxic necrosis of the epidermis).

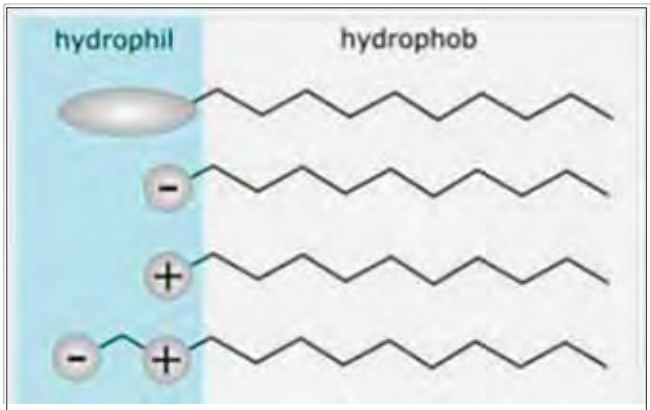
The surface lipid barrier can also be removed or damaged by excessive washing with highly "degreasing" solutions, which makes it easier for allergens and pathogens to pass through the epidermal stratum corneum.

Figure 4: Dog with severe oily seborrhoea and serious skin dysbiosis (copyright Dr. C. Noli).

The importance of the gut microbiome for skin health
It has been shown in humans (Ellis et al., 2019) and, to a lesser extent, in dogs (Pilla and Suchodolski, 2020) that proper **gut microbial balance** is necessary for overall immune health (Ruohtula et al., 2019). In fact, the gut microbiome is critical to the immune balance of the whole body, as billions of microorganisms interact daily with 90 percent of the body's lymphocytes and plasma cells, located right next to the intestinal loops.

This continuous communication between bacteria and lymphocytes trains the immune system to react most appropriately to external stimuli in every body area, including the skin, by tolerating harmless molecules (pollens, food antigens) while becoming reactive to pathogens. This is how a healthy gut microbiome is reflected in good skin health. Disruption of this mechanism due to gut dysbiosis has been associated with the development of allergies in humans (Lee et al., 2018), and preliminary data on gut dysbiosis in allergic dogs have also been published recently (Rostaher et al., 2022, Guidi et al., 2021).

How to maintain the balance of the skin and gut microbiome
Adopting good dermatological care habits is crucial for maintaining the balance of the skin microbiome in a healthy dog. First and foremost, it is essential to wash the dog exclusively with dog-specific high-quality **mild shampoos** that respect the epidermal ecosystem and contain not aggressive surfactants. This keeps the dog's skin clean and moisturised while removing dirt and excess sebum without harming the skin's surface lipid barrier, irritating the immunological barrier, or altering the balance of the microbial barrier.



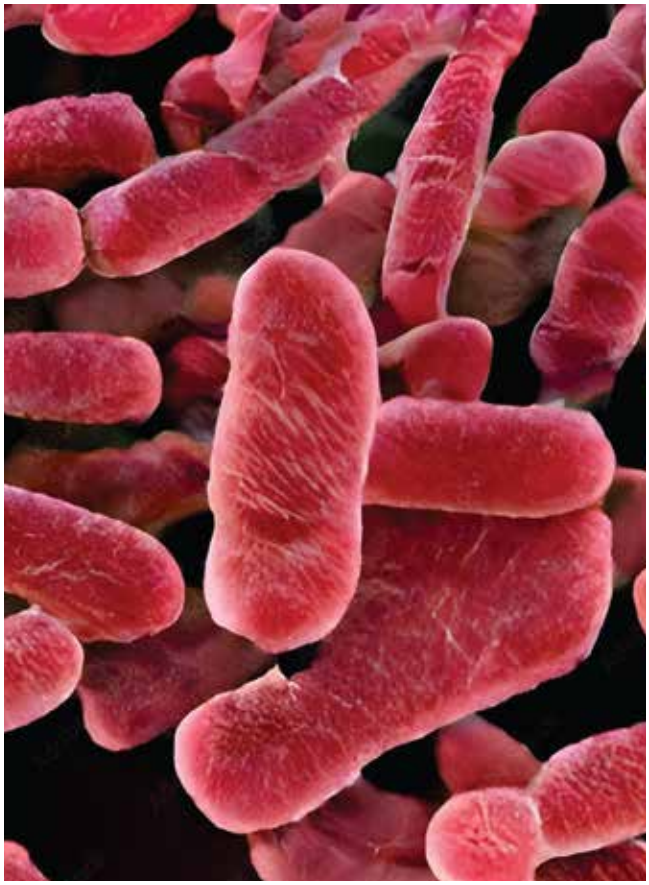
SURFACTANTS: Organic compounds having a hydrophilic "head", with an affinity with water, and a hydrophobic "tail", with an affinity with oil molecules. When surfactant molecules come into contact with water, they tend to associate to form aggregates called micelles that "solubilise" the oily materials in the dirt, making them easier to remove.

Secondly, it is important to feed the dog a **balanced diet** rich in nutrients vital for epidermal maturation and the production of the surface lipid film, such as amino acids, vitamins, and essential fatty acids, specifically to support the production of a healthy stratum corneum. As in humans, the gut microbiota in dogs can be modified by diet (Pilla and Suchodolski, 2021), and **nutritional interventions** (pre-, pro-, and post-biotic, as well as prescription diets) can be prescribed to correct gut dysbiosis (Wernimont et al., 2020). Treatment of gut dysbiosis may relieve the symptoms of allergic skin disease due to the tolerogenic effects of healthy bacterial flora on the immune system.
For the formation of the surface lipid barrier, healthy immune system function, and the balance of the skin microbiome, it is especially beneficial to have fibre, a vital source of nutrition for bacteria that digest it to produce short-chain fatty acids and sphingolipids (Pucheau-Haston et al., 2015).

Several studies have been published on the use of pre- and probiotics for human atopic dermatitis with controversial results (Sodré et al., 2022), while only a few studies have been performed in dogs (Marsella, 2009; Marsella et al., 2012). For example, atopic dermatitis was improved in a mouse model by oral administration of *Lactobacillus casei var. rhamnosus* (LCR35), which increased the intestinal population of *Bacteroides fragilis, Lactobacilli, Bifidobacterium* and *Enterococcus*, while the frequency of *Clostridium coccoides* was reduced (Yeom et al., 2015).

The treatment also restored the Th1/Th2 balance. In a prospective placebo-controlled study, oral administration of the probiotic *Bifidobacterium animalis subsp lactis* (LKM512) relieved itching in adult AD patients (Matsumoto et al., 2007; Matsumoto et al., 2014). In a prospective randomised trial, oral application of *Lactobacillus salivarius* LS01 and *Bifidobacterium breve* BR03 for 12 weeks to adult patients with atopic dermatitis improved severity, quality of life, and the ratio of Th17 and Treg cells, while decreasing immune activation (Drago et al., 2015; Iemoli et al., 2012).

Alternative strategies can also be adopted to train the cutaneous immune system to respond appropriately to the agents it is exposed to, whether harmful (pathogenic bacteria) or harmless (allergens).



Lactobacilli shown through an electron microscope

For instance, it has been demonstrated that using **topical products containing** inactivated beneficial **bacteria** can lower the amount of *Staphylococcus aureus* and alleviate the clinical symptoms of atopic dermatitis in humans (Gueniche et al., 2006). A recent study in dogs based on the use of a spray containing tyndallised *L. rhamnosus* and *L. reuteri* (Linkskin) showed that, although no longer viable, these bacteria can interact with the skin immune system and modulate its response to allergens (Santoro et al. 2021).

In this study, dogs exhibiting signs of atopic dermatitis received daily treatments with Linkskin spray on glabrous regions (to maximise contact with the skin's immune system) for a month. Lesions and itching associated with skin allergies diminished throughout the month of treatment and in the four weeks following its conclusion, indicating a tolerogenic "normalisation" of the skin's immune system toward allergenic stimuli.

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