Derm Scientia

A distribution from the Dermatology Chapter of the Australian and New Zealand College of Veterinary Scientists

Welcome to the inaugural Derm Scientia

This communication has the broad goal of promoting the practice of evidence-based veterinary dermatology across Australia and New Zealand. Where evidence is lacking, expert-opinion will be drawn on. Brief summaries and quotes from recent/pertinent research, reviews and guidelines relevant to clinical dermatology will be provided, including links to free-access articles. The aim is for two distributions per year, and the focus is to keep content relevant to everyday practice. Distribution to veterinary colleagues and students is welcomed, with acknowledgement of the Dermatology Chapter.

MAIN TOPIC: Antibiotic Use in Skin Disease

Background Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) is present in Australia and both prior antibiotic use and concurrent immunomodulatory therapy are confirmed risk factors.[1,2] With few concerns about resistant skin bacteria in dogs and cats for many decades, habits such as reaching for antibiotics for non-specific skin presentations "just in case" or using multiple repeat courses of antibiotics without addressing the underlying disease developed in veterinary practices worldwide. "*The emergence of multi-resistant bacteria, particularly MRSP, has focused attention on the need for optimal management of superficial bacterial* (infection)" [3] "*Bacterial skin infections are one of the most common reasons for using systemic antimicrobials in dogs and cats. Appropriate management of these infections is therefore crucial in any policy for responsible antimicrobial use.*" [4] Resources to guide practitioners in the diagnosis, treatment and prevention of SBF are now readily available,[3-5] (Hillier et al. 2014; Beco et al. 2013a; Beco et al. 2013b), and prescribing habits and restrictions on antibiotic use have begun changing.[6]

A) How do bacterial skin infections present?

Superficial bacterial pyoderma (BP) is the most common form, where bacteria are located within the epidermis and/or hair follicles. It is distinct from surface infection (or bacterial overgrowth) where bacteria are located on the surface of the epidermis, and deep infections where bacteria are deep in the dermis, typically following rupture of hair follicles. Staphylococcal species are by far the most common bacteria involved in all forms, but a range of other bacteria may be more rarely involved.

Superficial BP produces a wide variety of lesions, including erythematous papules, pustules, crusts, erosions, alopecia (including 'moth-eaten' forms in short-coated breeds), erythema, epidermal collarettes, and hypo- or hyperpigmentation.[3,4] (See images: Hillier et al. 2014; Beco et al. 2013a) Surface infection/bacterial overgrowth may affect body regions or skin folds (intertrigo), and commonly produce erythema, greasy exudate and odour. Deep BP typically presents as erythematous nodules or swelling with draining tracts, and haemorrhagic or purulent discharge.[4]

B) How is bacterial pyoderma diagnosed?

Clinical signs may be suggestive of BP, but distinction of superficial from surface forms, and BP from other skin diseases is not readily made based on lesions alone; "*the diagnosis must be confirmed using cytology.*" [4] "*Demonstration of cocci from lesional skin by cytology is a powerful adjunctive diagnostic test and is strongly encouraged for proper diagnosis.*" [3] "*Cytology is also essential for the diagnosis of co-infection with Malassezia pachydermatis*" (common) *or rod-shaped bacteria (rare) in dogs with superficial BP.*" [3]

Cytology is particularly essential when:

(i) typical lesions (pustules) are not present or scant and pyoderma is still suspected
(ii) typical lesions are present but there is a poor response to empirical antibiotics
(iii) bacterial culture is performed … positive culture with negative cytology does not confirm infection and may reflect normal microbiota, and negative culture with positive cytology does not exclude infection

Cytology methods: "*There are a number of different methods.*" [4] (See details/images): Beco et al. 2013a). In many cases, cytology readily confirms the absence or presence of bacterial infection. Key findings are:

- Absence of BP
  - Neutrophils are common with any skin damage as part of the repair response to skin insults
  - Neutrophils without bacteria (or only occasional focal bacteria) mostly indicates no infection*
- Superficial BP
  - Neutrophils with associated bacterial cocci mostly indicates infection
    - "*The presence of coccoid bacteria from typical lesions is highly supportive* (of BP)" [4]
    - "*… with inflammatory cells and intracellular cocci .. infection is confirmed.*" [4]
  - Neutrophils predominate in most cases of pyoderma, and nuclear streaming is common as cells are fragile and vulnerable to trauma.[4]
  - Neutrophils may be absent with immunosuppressive diseases or treatments e.g. glucocorticoids.[3,4]
- Surface infection/bacterial overgrowth
  - large numbers of bacteria with few or no neutrophils[4]
- Deep BP*
  - Neutrophils with intracellular bacteria indicates infection
  - Bacteria may not be as readily detected as with surface and superficial forms: careful searching for bacteria may be required, particularly if there is associated scarring.[4]

C) When are antibiotics indicated for skin diseases?

In general, antibiotics are not indicated for skin disease unless there is cytological (or histological) evidence of bacterial infection (cocci, neutrophils).
"*Antimicrobials should not be speculatively used on the basis of the clinical signs only.*" [4]

The exception may be classical, extensive and/or deep lesions in patients with immunocompromise (including those on glucocorticoid or Apoquel® therapy). When in doubt, consider topical antiseptics (see below) for superficial lesions, and reassess after 1-2 weeks, or biopsy for histopathology +/- C&S for nodular presentations that may be deep BP. Seeking an early second opinion for atypical cases can be beneficial.

D) What are the optimal empirical antibiotic choices when antibiotics are indicated?

"*Once pyoderma has been diagnosed, it is important to consider if the infection is deep, severe and/or generalised enough to warrant treatment with systemic antibiotics.*" [5]
Thus, clinical factors in combination with cytology are important to guide optimal treatment choices. Preferred alternatives for mild, surface and/or focal infections include topical antimicrobial shampoos and sprays, or potentially topical antibiotics if antiseptics are not effective.[5]

Topical antiseptics: "*Topical antiseptic treatments can hasten clearing of infections, or will greatly reduce the need for systemic therapy.*" [5] Chlorhexidine (4%) shampoo twice weekly with chlorhexidine 4% solution on lesions once daily was equally effective as systemic antibiotics for treatment of SBP in a randomised blinded study.[7] (Borio S et al. 2015) Solutions (e.g. Chlorhex-C®; not scrub formulations such as Chlorhex-S®) or leave-on formulations (e.g. Pyohex® Medicated Conditioner or Resichlor® Leave-On Lotion) applied to skin without rinsing off provide maximal residual action. Chlorhexidine solution is typically commercially available at 5% concentration; requiring dilution 1:1 (1-part chorhex to 1-part water) for 2.5% solution, and 4:1 for 4% solution. Solutions of 2-3% chlorhexidine are effective in-vitro against *S. pseudintermedius* and appear effective for SBP, but the comparative efficacy to 4% solution is not reported. Chlorhexidine does have the potential to irritate skin in a minority of patients, with erythema, scaling and pruritus reported.[7] Initial use on a test area may be prudent for thin, fragile, sensitive skin (e.g. axillae/groin especially in older

patients, or with severe skin barrier defects). The use of moisturising conditioners may reduce irritation due to drying effects of chlorhexidine.

Topical antibiotics: Topical fusidic acid or mupirocin are considerations for localised superficial BP,[3] although concerns over exposure potentially increasing resistance in human staphylococcal infections have been raised more recently. Antiseptic use is considered preferable wherever possible. Use of antibiotic-containing anti-inflammatory lotions (e.g. Neocort®, Apex® antibiotic lotion) is widespread in veterinary practices and may also promote antimicrobial resistance. Use of topical steroids alone (e.g. Cortavance®, human mometasone formulations) is likely more suitable. (Topic for Next Newsletter!)

Systemic antibiotics: Antibiotic tier groups have been developed to guide appropriate systemic antibiotic choices based on (i) likely efficacy for the infection in question; (ii) likely risk of antimicrobial resistance development; and (iii) importance for treatment of human infections. Currently there is incomplete consensus and some geographical variation in designation of antibiotics into these tier groups.[3,5] The World Health Organisation provides a biennially updated ranking of antimicrobials based on their importance for human health and risks of increased resistance from non-human use. Currently amoxicillin-clavulanate (amoxi-clav), 3rd generation cephalosporins (e.g. cefovecin) and fluoroquinolones are ranked highest as critically important antibiotics that should only be used prudently in human and veterinary medicine. Within the 2nd rank (highly important antimicrobials) are 2nd generation cephalosporins (e.g. cephalexin), lincosamides (e.g. clindamycin), sulphonamides and tetracyclines.[8] (WHO 2018)

First-line antibiotics There is general consensus that β-lactams (**cephalexin** 22-30mg/kg BID or **amoxi-clav** 20-25mg/kg BID) are good first-line choices suitable for empirical therapy of BP assuming a diagnosis is confirmed (e.g. cocci +/- neutrophils on cytology).[3,5] However, the WHO risk ranking as above considers amoxi-clav as critically important,[8] and it has also been associated with higher rates of detection of multi-drug resistant (MDR) E-coli post-therapy than cephalexin,[9] which may suggest cephalexin is the optimal first line choice for BP; a concept not yet raised in the veterinary dermatology literature. **Clindamycin** is also considered a first line choice,[3,5,10] with once daily dosing potentially optimal (11mg/kg).[10] However, it may be less frequently effective for BP than β-lactams, as *S. pseudintermedius* is often reported with lower in-vitro susceptibility to clindamycin compared to β-lactams,[3,10] and inducible clindamycin resistance is known to occur during therapy[11] (although clindamycin use may have the advantage of promoting clindamycin-resistance alone and not multi-drug resistant infections).

E) What if empirical therapy is ineffective?

The first step when faced with poor response to therapy is always to reassess the diagnosis. Has anything been missed? Has compliance been effective? Is cytology still consistent with infection?

For antibiotic resistance to be a consideration, cytology must confirm the presence of cocci while the patient is still on antibiotics. Other common reasons for poor clinical response to appropriate empirical antibiotic therapy include yeast overgrowth while on antibiotics, and persistence of an active underlying disease (e.g. demodicosis, allergies) even though initial BP has been cleared.

If persistent BP is confirmed on cytology and other possible causes for treatment failure are excluded, culture and susceptibility testing (C&S) is indicated. C&S may also be indicated where there is higher risk of MRSP (e.g. repeated antibiotic courses, other pet carriers, some geographical regions).[3,5] Culture swabs can be used to sample punctured pustules if present or rubbed vigorously for 5-10 seconds on representative superficial lesions that are positive on cytology (i.e. bacterial cocci +/- neutrophils), before placing in transport media.[4] (See details/images: Beco et al. 2013a)

Concurrent cytology is always essential to guide interpretation of C&S results.[4] Of note, there may be multiple different strains of *Staphylococcus* spp. involved in one particular infection, including MRSP and methicillin-susceptible (MSSP) strains concurrently. Sampling multiple lesional sites may increase the chances of accurately identifying all relevant causal bacteria.

Second-line antibiotics can be used *"when there is culture evidence that first-line drugs will not be effective."* They are considered "*not appropriate for empirical antibiotic treatment.*" [5,12]
Use of second-line options for BP in patients with poor tolerability of first-line options is also a consideration but should similarly be guided by C&S testing due to lower potential efficacy.

- **Trimethoprim sulphur** (15-30mg/kg BID) is a potential second-line choice assuming C&S results support efficacy; it can also be effective for some MRSP. Potential side effects, particularly with longer use as required for deep pyoderma, include hypothyroidism, reduced tear production, and auto-immune responses.[5]
- **Doxycycline** should be considered a second-line option, despite not uncommonly being used empirically for skin disease, as *S. pseudintermedius* is typically reported with higher levels of in-vitro resistance to tetracyclines, yet some MRSP/multidrug-resistant staphylococci may be susceptible.[3,5] Appropriate use of doxycycline for skin disease could arguably be reserved for susceptible MRSP infections. Use in anti-inflammatory roles is now increasingly discouraged.

Third-line antibiotics are considered critically important to animal and human health for treatment of multidrug-resistant bacteria, and with risks of developing resistance towards these drugs, their use in veterinary patients is of great concern. They should only be considered when C&S indicates resistance to all first and second-line options.[5,12] Two third-line antibiotics within this highest priority, critically important antimicrobial group which are not uncommonly used for skin disease in dogs and cats are: [8,12,13]

- **Fluoroquinolones** (e.g. enrofloxacin, marbofloxacin, pradofloxacin) are documented with increasing levels of resistance to *Staphylococci* spp., probably due to their common usage, and any indication for superficial BP is now questioned.[3,5] Their use for skin disease may ideally be reserved for resistant deep BP with no other antibiotic options.
- **Cefovecin** (Convenia®) - a 3rd generation cephalosporin (not equivalent to 2nd generation cephalexin). "*Cefovecin is often an appealing antibiotic choice in cats because of its long duration of action … but its use in the treatment of common feline conditions that can be successfully treated without antibiotics or with narrower spectrum antibiotics needs to be questioned.*" [12] (Whitehouse and Viviano 2015) Rapid development of E-coli resistance to cefovecin when cultured in sub-inhibitory antimicrobial concentrations,[13] and higher rates of MDR *E-coli* post cevofecin-therapy,[9] raise further concerns that cefovecin may similarly promote staphylococcal resistance, further supporting these recommendations.

Other potential antibiotics of critical importance to human health include rifampicin, amikacin, azithromycin, ceftazidime, chloramphenicol, clarithromycin, florfenicol, imipenem, and piperacillin. There use in veterinary patients is strongly discouraged and limited to life-threatening diseases under expert care.[5,6]

IN SUMMARY

- **Topical antiseptics** should be considered first-line therapy for confirmed superficial BP, especially if localised, and also when superficial BP is unconfirmed.
- **Cephalexin,** and potentially amoxicillin-clavulanate and clindamycin are **first-line choices** suitable for empirical systemic therapy, assuming infection is confirmed, and topical therapy has failed or is impossible in that patient.
- **Use of other systemic antibiotics for BP should be guided by C&S testing.**
- **Fluoroquinolones or cefovecin are not acceptable first-line options, and their use should be restricted to cases where C&S indicates no other choices.**
- Optimal choice of antibiotics is based first and foremost on the most effective antibiotic for the infection in question together with its importance in relation to antimicrobial resistance.
- Ability to administer and ease of compliance are of secondary importance: consideration should always be given to ways of administering first-line options in preference: **ease-of-use alone does not justify routine use of second or third-line options.**

F) What about concurrent use of anti-inflammatories?

Irrespective of underlying allergy, treatment of BP with systemic antibiotics is ideally performed without concurrent immunosuppression, especially glucocorticoids or oclacitinib (Apoquel®) concurrently during the antibiotic course. Concurrent immunosuppressive drugs is a recognised cause of poor response to treatment of BP.[5] *"Concurrent glucocorticoid use during therapy of BP is strongly discouraged because it may improve the clinical appearance of the lesions and result in premature discontinuation of antibiotics whilst also reducing the patient's innate and adaptive immune response to infection."*[3] Brief initial anti-inflammatory therapy for the first few days of antibiotic treatment may be appropriate when there is severe patient pruritus, although rapid reduction of pruritus with appropriate antibiotics alone often occurs. Lokivetmab (Cytopoint®) should not impact antibiotic efficacy nor alter pyoderma lesions or assessment of antimicrobial response. However, it's efficacy for the treatment of pruritus from BP alone is not described.

G) What about recurrent bacterial pyoderma?

Addressing the underlying cause of BP (most commonly allergies) is essential to limit recurrences, with consideration of further diagnostics and/or management plans always indicated. Pulse antibiotic therapy and repeated courses of antibiotics without addressing the underlying cause encourage development of antibiotic resistance and are strongly contraindicated.[3,5] When the primary cause is not readily resolved, topical antiseptic prevention plans and on-going allergy treatment plans are typically indicated.

ALLERGY SNIPPETS

1. *Toxocara canis* IgE in atopic and non-atopic dogs[14] (Zwickl et al. 2018):

Background Total IgE concentrations are higher in dogs than humans. Persistent *Toxacara canis* (roundworm) larval infection is prevalent in dogs and associated with substantial specific antibody levels. Potential correlation between total and *T. canis*-specific IgE in dogs was previously unevaluated.

Study Serum from client-owned dogs with atopic dermatitis (30) and dogs without allergic skin disease or immunocompromise (30), of varying ages and breeds presenting to referral dermatology in Switzerland, were evaluated for total and *T.* canis-specific IgE levels. Serum from some dogs (20 atopic, 13 non-atopic) was also evaluated for allergen-specific IgE levels (Heska Allercept®).

- Total IgE and *T. canis*-specific antibody were significantly higher in non-atopic compared to atopic dogs
- Allergen-specific IgE was also significantly higher in non-atopic compared to atopic dogs, in contrast to some other studies. This emphasizes the limitations of allergen testing alone for diagnosis of atopy.
- 90% of dogs, including those undergoing regular deworming, had positive *T. canis*-specific antibodies, suggesting repeated exposure and/or lengthy persistence of antibody responses after exposure
- A positive correlation was demonstrated between *T. canis*-specific IgG and IgE, between total IgE and *T. canis*-specific IgG and IgE, and between total IgE and allergen-specific IgE

Summary *Toxacara canis*-specific IgE appears to be a major component of total IgE in dogs. Total and *T. canis*-specific IgE levels were higher in non-atopic compared to atopic dogs. It is possible *T. canis* infection may have a protective effect against the development of canine atopic dermatitis. Reduced frequency of anthelmintic therapy, potentially supplemented by monitoring of nematode burdens (e.g. faecal floatation), may be a consideration in dogs at higher risk of developing or with early signs of atopic dermatitis.

2. Pollen Allergens in Australia and New Zealand[15] (Haberle et al. 2014):

Background *"The composition and relative abundance of airborne pollen in urban areas of Australia and New Zealand are strongly influenced by geographical location, climate and land use."*

Study Retrospective evaluation of atmospheric pollen data from 11 cities (Darwin, Perth, Melbourne, Hobart, Canberra, Sydney, Brisbane, Kiakohe, Auckland, Christchurch, Dunedin).

- Grass pollens and Cypress family tree pollens were most abundant across all sites, making up over 50% of airborne pollens in urban environments
- Other tree pollens (Birch, Eucalyptus, Pine, Olive, Casuarina) and Weed Pollens (Plantain, Dock, Sorrel) were the next most prevalent

- Variation in pollen prevalence is associated with climatic factors
- Australian native plant pollens are poorly evaluated

Summary Pollen charts for geographical areas relevant to each patient, along with the seasonal history of signs in that patient, are used to guide selection of allergens for allergen-specific immunotherapy.

3. Hair and saliva analysis fails to accurately identify atopic dogs or differentiate real and fake samples[16] (Bernstein et al. 2019):

Background *"The availability of direct-to-consumer medical testing for human and veterinary health conditions has increased in recent years. For allergies, several companies market proprietary hair and saliva tests directly to pet owners. These tests have not been validated and there is limited regulatory oversight for such tests in veterinary medicine."*

Study Samples from normal animals (6 dogs, 1 cat), animals with confirmed AD (5 dogs, 1 cat), and synthetic fur and sterile saline (11) were submitted to a laboratory offering direct to client testing on saliva and fur samples to identify potential allergens.

- Results for samples from healthy and atopic animals were no different from each other or from synthetic fur or saline samples
- Reproducibility for paired samples was not different from random chance
- Results for animals correlated strongly with results for synthetic fur and saline ($r = 0.71$, $P < 0.05$)

Summary *"The direct-to-consumer hair and saliva test for pet allergies examined in this study performed no better than chance and the results were not reproducible."*

4. Apoquel® in Cats: preliminary studies

Background Oclacitinib decreases pruritus and lesions in allergic dogs and inhibits IL-31 induced pruritus in cats. Two small studies have now evaluated response to oclacitinib in allergic cats. NB Presumed atopic dermatitis in cats shares many clinical features with AD in dogs. However, as pathogenesis of this presentation in cats is incompletely evaluated it is currently variably referred to as AD, or non-flea non-food hypersensitivity, or atopic syndrome.

a. Prospective non-blinded non-controlled study in 12 cats with atopic dermatitis[17] (Ortalda et al. 2015)

Study Cats with AD were treated with oclacitinib 0.4-0.6mg/kg BID for 14 days then SID for 14 days. Response was assessed via clinician lesion scores, and client pruritus scores.

- Good improvement (both scores) in 5 cats
- Easily administered, well-tolerated in 10 cats

b. Double-blinded, randomized, controlled study in 40 cats with atopic dermatitis[18] (Noli et al. 2019)

Study Cats with AD were treated with oclacitinib (20 cats, 0.7–1.2 mg/kg) or methylprednisolone (20 cats, 0.5–1 mg/kg) orally BID for 28 days. (Oral methylprednisolone is available for veterinary use in Europe and is slightly more potent than oral prednisolone). Response was assessed via clinician lesion scores and client pruritus and quality of life scores. Biochemistry and haematology changes were evaluated in some cats.

- Both groups significantly improved (all scores) by day 28
- Improvement was slightly better (all scores) to methylprednisolone
- There were five non-responders to oclacitinib and 3 to methylprednisolone
- Four of 14 cats had mild increases in kidney function tests (oclacitinib group) and 3 of 12 cats had notably elevated ALT (methylprednisolone group)

Summary Apoquel® may be useful for treatment of AD in cats but higher dose rates may be required compared to dogs. Safety is not established and use in cats is off-label and cautioned, particularly with any history or increased risk of infectious, neoplastic and/or kidney disease.

5. Equine Insect bite Hypersensitivity: what's known?

European Academy for Allergy and Clinical Immunology Position Paper[19] (Pali-Scholl et al. 2019)

Review Article[19] (Schaffartzik et al. 2012)

Background Insect bite hypersensitivity (IBH) is the most common allergic skin disease of horses, caused by bites of blackflies, stable flies, hornflies, mosquitoes, deerflies, horseflies, and most importantly, the biting midge *Culicoides* spp.[19,20] The prevalence of IBH varies from 3% in Great Britain to 37.7% in Shire horses in Germany and 60% in Queensland, with an estimate of ~10% of horses affected worldwide.[19,20] IBH is considered a multifactorial disease with genetic and environmental factors contributing to disease onset and perpetuation:[20]

- Heritability has been estimated from 0.08 to 0.30 (NB heritability of 1 means genetics are the only factor influencing occurrence)
- Prevalence varies considerably with breed, and to a greater extent with lineage or family
- Prevalence varies with locality and climate: clay soils, woody vegetation, and warm dry climates with low wind speeds are reported to favour *Culicoides* spp. development

Immunopathogenesis:[19,20]

- IgE antibodies and Type-1 hypersensitivity response are confirmed, with 21 *Culicoides* salivary gland proteins characterised[19]
- Delayed type hypersensitivity is thought to also contribute to disease

Treatment:[19]

- Is currently largely reliant on insect avoidance (rugs, repellents, stabling), with or without systemic or topical glucocorticoid therapy
- Allergen-specific immunotherapy: early small studies using crude allergen extracts, and more recent evaluation using recombinant allergens have not demonstrated efficacy

Study Double-blinded, placebo-controlled randomised study of IL-5 vaccination in 34 Icelandic horses with IBH.[21] (Fettelschoss-Gabriel et al. 2018) Antibodies to IL-5 and statistically significant improvements in lesional scores were documented in the treatment group, and not the placebo group, with at least 75% reduction in lesions scores in 21% of treated horses and in none of the placebo group. Safety and long-term efficacy are unknown.

Summary IBH is common and challenging to treat. New treatment options are being evaluated.

Acknowledgements

That's our dose of scientific updates on veterinary dermatology for this distribution. Contributors to this edition were Allan Bell, Sonya Bettenay, Greg Burton, Peter Hill, Rob Hilton, Ken Mason, Beth McDonald, Ralf Mueller, David Robson, Meng Siak, Ruth Sutcliffe, and Linda Vogelnest. We also acknowledge all authors who contributed to the research and publications for improving our knowledge in veterinary dermatology. Although we recognise veterinary practice has many challenges, including variable financial, practical and time constraints for owners, we encourage veterinarians at all levels to increase the practice of Science within our profession. Aim to break perpetuated habits that don't have scientific merit and endeavour to increase the practice of evidence-based veterinary dermatology.

I welcome feedback and topic requests for the next distribution.
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Sincerely
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