Australian and New Zealand College of Veterinary Scientists

Dermatology Chapter
Science Week Proceedings
11\textsuperscript{th} & 12\textsuperscript{th} July 2014

The Changing Face of Veterinary Dermatology:
New Challenges, New Technologies
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The Dermatology Chapter of the Australian and New Zealand College of Veterinary Scientists would like to thank Merial for their generous sponsorship of Chapter scientific programs and social events in 2013-14.

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Science Week, Gold Coast 2014
11th Annual Dermatology Chapter Meeting of the Australian New Zealand College of Veterinary Scientists

At our regular Gold Coast Venue we have 2 days of state of the art dermatology. The changing face of veterinary dermatology and meeting those new challenges is the focus of this year’s science week program.

Recent changes and advancements in treatment options for common dermatological conditions has led veterinary dermatologists to explore other treatment modalities such as laser therapy. On the first day of this meeting we welcome Dr Mona Boord from San Diego to give an introduction to the use of laser therapy as it applies to dermatological practice.

Meeting some of these new challenges involves revisiting some older treatment options with a new focus. David Robson will present an extensive commentary on the state of anti-histamine use, while Ted Whittem will remind us all about the use and action of shampoos.

Day two, Mona Boord concludes her presentation on pododermatitis with a lecture on surgical therapy. Mona is also presenting an update on the management of the common autoimmune disorder, pemphigus.

The reminder of the lectures address the important topic of MRSP. The dermatology chapter has gathered an international group of experts to discuss the emergence, diagnosis and management of bacterial resistance. These lectures will be of great value to all veterinarians where ever their special interests may lie.

We conclude our program with 3 presentations from current residents in dermatology.

Karyn Wesselingh
Beth Macdonald
Peter Hill
(Dermatology Chapter Science Week Coordinators)
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**Biographies**

**Mona Boord**
Dr. Mona Boord graduated from the University of California Davis in 1992. She started a private practice internship focused on internal medicine, emergency medicine, surgery and dermatology with the goal of becoming a veterinary surgeon. She spent many hours performing surgery, but ultimately found the work repetitive. Her internship was with her wonderful mentors and now partners Dr. Craig Griffin and Wayne Rosenkrantz. She experienced the world of dermatology and her interests changed. Dr. Boord was asked to stay on with Animal Dermatology for her residency and she completed her residency becoming a Diplomate of the American College of Veterinary Dermatology in 1997. She has been with the Animal Dermatology Clinics in San Diego since graduation and finds this work extremely fulfilling. She has brought her previous love of surgery to the field of dermatology.

**Evie Knight**
Evie Knight graduated from the University of Melbourne in 2010. She completed a rotating internship at Pet Emergency and Queensland Veterinary Specialists during 2011. After the internship she spent the next few months in general practice before starting an internship with Dermatology for Animals in early 2012. She started her residency this year.

**John Hutt**
John graduated from the University of Queensland in 1988. He worked in general practice in Brisbane for 18 months before travelling to the UK in 1990, where he worked in a small animal practice for the next 11 years. During this time he developed an interest in veterinary dermatology. He was awarded the RCVS Certificate in Veterinary Dermatology in 1997, and worked as clinical assistant in dermatology at the Animal Health Trust from 1998 to 2000. John is a past President of the British Veterinary Dermatology Study Group. In 2001 John set up North Kent Referrals, a multi-disciplinary referral practice in the south of England, and he owned and ran the practice until its sale in 2012. In 2006 John was admitted to membership of the Australian College of Veterinary Scientists (MANZCVS) by examination in small animal medicine. Following his return to Brisbane, John joined the team at Dermatology for Animals as Resident in Dermatology in July 2013. Outside of work John's major interest lies in English Literature and in 2006 he completed a Bachelor of Arts at the Open University.

**Rusty Muse**
Dr. Rusty Muse received his Doctor of Veterinary Medicine degree from Louisiana State University and completed his residency at Animal Dermatology Clinic—Tustin (California) and the University of California-Irvine Department of Dermatology in 1995 and became board certified in veterinary dermatology as a Diplomate of the American College of Veterinary Dermatology (ACVD) in 1996.

Dr. Muse is co-owner of the Animal Dermatology Clinics in the US and in Perth, Australia and an Executive Board member of the Animal Dermatology Clinic Management Group. Dr. Muse currently serves as past president on the Executive Board of the ACVD after serving as President for the last two years. Dr. Muse is a registered specialist in dermatology in Western Australia and practices in Perth in partnership with Dr. Amanda Burrows as Animal Dermatology Clinic-Perth with locations at Murdoch University School of Veterinary Medicine and Perth Veterinary Specialists. Dr. Muse is also the current sub-chair for publicity for North America for the 8th World Congress of Veterinary Dermatology to be held in 2016 in Bordeaux, France. He is also a member of the Australian and New Zealand College of Veterinary Scientists Dermatology Chapter, American Academy of Veterinary Dermatology, Southern California Veterinary Medical Association, and Kentucky Veterinary Medical Association. Dr. Muse also travels to satellite locations in Albany, Geraldton, and Broome in WA.
Jacqueline Norris
Passionate about teaching clinically relevant infectious disease courses for veterinary undergraduates, veterinary practitioners and companion animal breeders that are centred on the relationship between host, pathogen and environment and how each is involved in the development of disease in animals (including humans).

Her research reflects a broad interest in infectious and non-infectious diseases. This includes: **Companion animal viral diseases** (especially Feline Infectious Peritonitis, Feline Calicivirus, Feline immunodeficiency virus, Canine Parvovirus, Canine Distemper virus); **Q fever** (how common is it in the veterinary personnel and animal owners, what are the risk factors for exposure? What role do companion animals play?); **Multi-resistant Staphylococcus species** – what role do these Staphylococcus species play in companion animal disease (cats, dogs, horses), what are the preventable risk factors and the risks to health in human communities (pet owners, pet breeders, and veterinary personnel)?; and **Chronic Renal Disease in Felids (big cats eg Lions; and domestic cats)**- development of strategies for early diagnosis, targeted treatments and prevention.

Darren Trott
I completed my veterinary degree at Murdoch University and worked in small animal practice for eight years. Following an honours project on *Listeria monocytogenes* I became interested in the ecology of infectious diseases and completed a PhD with Prof David Hampson on intestinal spirochaetes (awarded in 1998). After completing a three year post-doc at the National Animal Disease Center in Ames, Iowa, USA, I accepted a lectureship at The University of Queensland (UQ) School of Veterinary Science in 2000. I taught veterinary microbiology to veterinary undergraduates at UQ for 10 years and conducted research on gastrointestinal diseases, microbial ecology and virulence/antimicrobial resistance in companion animal, livestock and human bacterial pathogens. I joined The University of Adelaide School of Animal and Veterinary Sciences in January 2010 and my research areas have expanded to also include the development of new antimicrobials for superbug infections.

Ted Whittam
Ted received his BVSc in 1980 and followed this with 8 years in private veterinary practice. He then studied for his PhD in veterinary pharmacology from the University of Georgia from 1988 to 1991 following which he held academic appointments at Massey University and University of Illinois. After an 8 year sojourn as a researcher in the pharmaceutical industry, in 2008 Ted was appointed Professor of Veterinary Clinical Sciences and Associate Dean for Clinical Programs at the University of Melbourne. Ted is a Diplomate of the American College of Veterinary Clinical Pharmacology and a Fellow of the Australian and New Zealand College of Veterinary Scientists in veterinary clinical pharmacology. He served one term as president of the American Academy of Veterinary Pharmacology and Therapeutics from 2003-2005. He is a member of the Editorial Board of the *Journal of Veterinary Pharmacology and Therapeutics* and he is Associate Editor for *Clinical Case Reports*. Ted’s research focuses on novel solutions in veterinary pharmacokinetics, and the conduct of veterinary clinical trials. He has supervised or supported 29 research Masters and 8 PhD degree candidates.
Can a laser help my practice?
The laser is a tool which will augment your diagnostic and therapeutic options. There are many procedures that can be performed more easily with the laser than with traditional surgery. There are also procedures that cannot be done or wouldn’t normally be attempted with traditional surgery. The laser will also enhance the public image of a practice. The public is well educated and desires less painful alternatives to traditional surgery for their animal companions. Improved healing and increased comfort are non-economic factors that may lead to increased numbers of procedures and referrals.

How do lasers interact with tissue?
The energy from the laser light is transferred to the tissue. Depending on the wavelength of the laser light, the optical properties of the irradiated tissue and the technique of the surgeon, the laser energy interacts with the target tissue.

There are different types of lasers available, which produce different wavelengths of light, different beam intensity, and different temporal patterns of the laser beam. In the understanding of how to use a laser properly, some time needs to be spent in understanding these terms. The other factor affecting the choice of laser is the composition of the tissue to be treated.

The wavelength of the beam depends on the lasing media. The lasing media is usually the product the laser is named after. For example, in a CO\textsubscript{2} laser the lasing media is CO\textsubscript{2} and it produces a wavelength of 10,600nm. This wavelength is in the infrared range and is invisible to the human eye. Helium neon was the lasing media of the older red laser pointers. Argon, Krypton and potassium titanyl phosphate (KTP) lasers produce light in the blue green range. Eximer lasers produce light in the ultraviolet range. There are dye and diode lasers with adjustable wavelengths.

The beam intensity is the amount of energy per area of tissue. Using the CO\textsubscript{2} laser as an example, a 10 watt laser applied into a 2mm tip will deliver 320 Watts/cm\textsuperscript{2}. This is only enough to warm tissue. A CO\textsubscript{2} laser needs to deliver 4500’5000 Watts/cm\textsuperscript{2} to ablate tissue efficiently. A 10 Watt laser through a 0.8mm spot will only deliver 2000 Watts/cm\textsuperscript{2}. Changing to a 0.4mm tip will increase the beam intensity to 8000 Watts/cm\textsuperscript{2}.

The interactions of laser light with tissue include:
1. Reflection of light without penetration of the target tissue
2. Transmission of light through the tissue
3. Scattering of light within the tissue
4. Absorption into the tissue and transforming the energy into a photo-thermal reaction
5. Photo disruption where the high energy pulse generates a shock wave
6. Photochemistry is which the light energy reacts with a chemical and stimulates a chemical process in the tissue

What determines which of the above interactions that will occur is based on the composition of the target tissue and wavelength of the light beam. The various wavelengths are preferentially absorbed by tissue based on the tissue’s composition. Thus a laser is chosen for a procedure based upon the optical properties of the target. In our case, this is skin. Tissues have different energy absorption coefficients based on their water, hemoglobin, melanin, and protein contents. Melanin and hemoglobin are present in the skin. Tissues of this color absorb blue and green wavelengths but not red wavelengths. Therefore a krypton or KTP laser is a better choice to remove a port wine stain or an angiomatosis lesion. Water is clear but does absorb light of longer wavelengths in the infrared range. Also the shorter the wavelength, the deeper the light beam may penetrate tissue. This may cause damage to tissues deeper than the target tissue and must be taken into account. Therefore the best laser for a procedure depends upon what type of tissue is being lasered. The CO\textsubscript{2} laser is very nice as it does not penetrate tissue deeply. This allows very precise dissection of tissues during surgery.

For most lasers the energy delivered to the target tissue creates heat (Photothermal reaction). The longer it takes to cut or vaporize tissue the more time the peripheral tissue is heated. This may create collateral thermal damage and delay wound healing. The absorbed light denatures proteins, causes mitochondrial swelling and vacuolization thus at
some point causes irreversible cellular damage. The hyperthermia may also destroy adjacent blood vessels. The goal with proper use of the laser is to reach a tissue temperature of 110 – 150 degree C quickly without superheating the tissue. As this temperature is reached the tissue will contract and char will form. The char is the remaining cellular contents once hydrogen, oxygen and nitrogen have been vaporized. The char changes the optical properties of the tissue and will affects energy absorption and transmission. Therefore time should be taken during surgery to wipe away char buildup.

**Thermal relaxation** is the time it takes for tissue to cool. This knowledge has been utilized to produce lasers with different temporal patterns to deliver pulsed beams versus continuous beams of energy. This allows improved surgical precision and decreases unwanted collateral tissue damage. By applying a high energy in rapid pulses there is specific selection of the energy being delivered to the specific tissue selected and not the surrounding tissue. There is a higher pulse of energy allowing the target tissue to reach the vaporization temperature quickly and then there is a brief discontinuation of energy applied to the tissue allowing adjacent cells to cool thus decreasing peripheral tissue damage and improve wound healing. This can be compared to cryotherapy in which multiple freeze thaw cycles are much more effective to necrotize a mass than a single freeze thaw cycle and similarly with multiple freeze thaw cycles there is less peripheral damage to “normal” tissue.

**Which laser is best for which type of tissue?**

CO₂ has a very long wavelength of 10,600nm. It is highly absorbed by water creating a photothermal interaction. This results in vaporization of the tissue with high water content with minimal scatter, shallow penetration, and minimal peripheral tissue injury. These features make the CO₂ laser very useful for most cutaneous procedures. Due to the long wavelength of the CO₂ laser, it can only be delivered by hollow waveguides and articulated arms; therefore, it cannot be utilized for endoscopic procedures. Argon and KTP lasers have short wavelengths of 524 and 532nm respectively. For tissues high in hemoglobin, argon lasers and KTP lasers are preferentially absorbed. The problem with these lasers is their short wavelength allows them to transmit through tissue that does not have high hemoglobin content. This can result in peripheral thermal tissue injury. To minimize damage the amount of energy delivered to the target tissue should be closely monitored. Between these two lasers are diode lasers and neodymium yttrium aluminum garnet (Nd:YAG) lasers with wavelengths of 635 – 740nm, and 1,064nm respectively. Water and hemoglobin will absorb these wavelengths but the CO₂ laser is better absorbed by water and argon is better absorbed by hemoglobin. The more specific the laser wavelength is for the type of tissue the less energy needs to be applied and therefore the depth of thermal injury to surrounding tissue is less. Dye lasers have variable wavelengths of 400 – 1000 nm depending on the dye. They have been used together with photosensitizers for photodynamic therapy. Eximer lasers have very short wavelength in the ultraviolet range and are popular in human dermatology cases to treat psoriasis and vitiligo.

Overall, for the most daily procedures in the veterinary dermatology practice, the CO₂ laser is the laser of choice.

**What are the risks or safety issues when using laser in the veterinary practice?**

With proper training and conscientious adherence to safety protocols the risks are very manageable. Most of the lasers being used in veterinary clinics produce heat and vaporization of the tissue. This creates a plume of smoke. The plume may contain viable organisms (bacterial or viral) as well as cells and can be irritating when inhaled. There are laser safe surgical masks available for use. The plume must be removed during the procedures with a smoke evacuator. The evacuator has a filter that should be changed based on hours of use. The surgical technician is responsible for logging the amount of time the evacuator is in use. Eye protection must be worn by all attending staff and the patient at the time of surgery. The type of eye protection will depend upon the type of laser being used.

As mentioned previously, there is heat generated by the laser, therefore surgical preparation should not include flammable products such as alcohol. Accidental fire can occur with flammable liquids, oxygen, paper drapes, or methane gasses. It is imperative to prevent endotracheal tube fires. There are laser-safe endotracheal tubes available or the practitioner can protect standard tubes with saline or sterile water soaked gauze when using lasers well absorbed by water. If surgery is being performed around the anal area, water soaked gauze should be placed in the anus.

If proper technique is not utilized, the surgeon, staff, or patient may receive accidental skin burns. Remember the laser is a light energy much like a laser pointer used in lecturing. If the laser pointer is aimed at a hole in the projection screen the light will continue on to whatever is behind it. When cutting through tissue it is common to cut through one area more quickly then another. If the laser is passed over the area already incised it continues on and burns the tissue beyond. This may be the surgeon’s finger or another tissue on the patient. Burns can be minimized by directing the beam at the surgical site, accurately using the foot pedal to activate the laser beam and using sterile water soaked
gauze or tongue depressors as a backstop. The surgical technician should put the laser in standby mode when not in use to prevent accidental discharge and burns.

The light from the laser can also be reflected and if reflected into the eye can create damage. Care should be taken not to aim the light at surgical instruments. There are laser instruments available with ebonized or burnished finishes which decrease reflected light. Personnel in the operating room must all wear protective eyewear. The type of eyewear needed varies with the type of laser. Regular glasses or safety lenses are sufficient for the CO₂ laser. The patient’s eyes should also be protected. Again sterile water soaked gauze may be placed over the eyes or there are special eye-cups and masks available.

For more information, the American National Standards Institute publishes a book of safety standards and regulations called *Safe Use of Lasers in Health Care Facilities*.

**What are the advantages of using laser over traditional surgery?**

One of the big advantages with most photothermal lasers is the sealing of small blood vessels. Using the laser provides a very dry surgical field even in highly vascular areas. A feline rhinectomy to remove squamous cell carcinoma may have taken 30 – 45 minutes with traditional surgery to control the hemorrhage, and with the CO₂ laser the procedure takes about 15 minutes.

Another very important benefit is decreased post-operative pain. The laser energy is painful at the time of surgery and general or local anesthesia must be used. However, post-operatively patients seem less painful and return to normal behavior more quickly. This can best be seen following a feline onychectomy or rhinectomy. The cats that have had a rhinectomy often are grooming and eating normally within 4 hours of their procedure. Subjectively, cats receiving traditional surgery for rhinectomy appear sensitive on their nose and don’t tend to eat for a day or two post-surgery.

Another benefit is decreased swelling. The laser energy does not crush or tear tissue; it vaporizes it. It also seals lymphatics thereby decreasing swelling. However if there is significant peripheral tissue damage due to incorrect use of the laser, thermal damage will result in additional tissue swelling and delayed healing.

Finally, the laser is a wonderful surgical tool that allows the veterinarian to offer surgical procedures that may be more difficult or not possible with traditional surgery techniques. The laser is an expensive tool but can certainly pay for itself in the dermatology clinic and probably pay for itself more easily in the general practice.
Lasers: Case Presentations
Mona J Boord, DVM, Diplomate ACVD,
Animal Dermatology Clinic San Diego

What are the applications for the laser in veterinary dermatology?
The focus in this lecture will be the use of the CO2 laser and my personal experiences and cases. The laser can be used for almost any procedure for which typical cold steel surgery is used. However where it comes in most useful is when a patient has multiple small lesions, lesions in highly vascular areas, or to remove proliferative tissues to promote healing.

The CO2 laser has been very helpful in patients that have multiple epidermal lesions to be removed. Depending on size, these lesions once removed can heal by secondary intention as quickly as lesions closed with primary closure. Examples of more common lesions would include multiple sebaceous adenomas, hemangiomas, keratoacanthomas, and feline ceruminous cystomatosis. There are multiple breeds in which multiple sebaceous adenomas can affect the quality of life due to pruritus and secondary infections. The removal of these lesions can significantly decrease the requirement for medical therapy. The time required to remove multiple small lesions with traditional surgery is more time consuming due to the need in most cases for primary closure. The laser provides a sterile eschar and allows healing by second intention for most smaller lesions. Another example seen commonly with multiple lesions are white skinned sun bathing dogs that develop multiple hemangiomas. The recommendation is to remove the lesions that have become raised as a papule or nodule, but these dogs can have dozens of tiny macular lesions. With the laser it takes very little time to ablate these small macular lesions present at the time of surgery and prevent the need for future surgery for some time.

The laser is also very helpful in removing epidermal lesions difficult to close with primary closure, and in some cases laser is the only therapy with good success. Feline ceruminous cystomatosis is an example. This is an entity in which multiple fluid filled ceruminous cysts form initially on the tragal folds of the pinna. If left untreated, the cysts extend down into the canal, occlude the canal, and secondary otitis externa and/or media develops. The cystic tissue is very thin and often adjacent to the pinnal cartilage. This makes removal of the entire cyst difficult with traditional surgery and without the removal of the entire cyst recurrence is likely.

Depending upon the laser and the video otoscope unit, laser may be performed within the ear canal to vaporize masses or the base of the masses. This can be performed at the time of the biopsy of the tissue. Often it is not known at the time of the surgery if the mass being removed is simple proliferative glandular tissue versus an adenoma or other neoplasm. Ablating the base of the mass and area around it may prevent recurrence if the biopsy report reveals a neoplasm. Another example of a lesion best removed with laser is cutaneous angiomatosis. In veterinary patients, due to the progressive proliferative nature of this condition, previous recommendations included wide surgical excision or amputation. If the lesions occurred in a location where this was not possible (such as the face) the pets were euthanized. Laser therapy has been reported to be a successful alternative in these cases.

Highly vascular areas are more easily handled using the laser. One of the more common procedures it has been recommended for is feline rhinectomy and/or pinnectomy secondary to squamous cell carcinoma (SCC). In the hands of an experienced laser surgeon, this procedure takes about 15 minutes, with more hemorrhage occurring from the sutures than the tissue removal. The size of the lesion is important with nasal SCC. The earlier these lesions are removed and the more aggressive the surgical margins will affect the recurrence rate of these cancers. The author prefers to remove the nasal tissue up to the junction of the nasal bone and cartilage dorsally. It is also better to remove a bit more of the upper lip filtrum than appears affected. Masses may be removed or biopsied from the nasal or oral cavity. Remember care must be taken when oxygen is being administered. A very problematic complication can be a tracheal tube fire. The laser can be used to remove neoplastic tissue on the penile sheath or perianal tissue with less pain and hemorrhage. Pinnectomy is a very quick procedure in the cat and only slightly more difficult in the dog. The laser beam can be used on low to draw the incision line. Remember the tissue is thin and the surgeon’s hands should be protected with moist gauze. After the first pinna is removed it can be used as a template for the second pinna so the patient is symmetrical post surgery.

Precision tissue removal can be performed with the single pulse mode on the laser. This is useful for actinic changes on the eyelid margin and distichiasis removal.
Infected tissue can be vaporized or removed using the laser. Surgical technique is very important so that the healthy tissue to remain is not contaminated with infected cells. The types of infections where this is important include papilloma virus, herpes dermatitis, mycobacterial granuloma and sarcoïds. The utilization of the laser with proper surgical technique has resulted in decreased recurrence rates post therapy. Typically there is a “clean pack” and a “dirty pack”. The idea is that the laser vaporizes the incision, minimizes hemorrhage and lymphatic contamination and sterilizes the surgical margins. Any instruments that touches the infected tissue are set aside and the surgical site is closed with clean gloves and instrumentation. Lepromatous dermatitis is a nodular disease caused by a mycobacterial organism thought to be spread by biting insects. These dogs are usually short coated and present with growing nodules on the pinnae or nasal planum however lesions may become widespread. Medical therapy is available but long term medications with rifampin and clarithromycin in large breed dogs not only is very expensive but some patients cannot tolerate the therapy. Surgical removal of these lesions may be more cost efficient and successful but a controlled study needs to be performed.

Another type of infected tissue includes chronic proliferative infected tissue. This is most commonly seen in cases of chronic otitis in certain breeds. If this problem is identified prior to calcification of the ear canal occurring, the duration of medical therapy may be shortened or total ear canal ablation may be avoided. Once the deep folded cauliflower like tissue is removed medical therapy is much more effective. The laser has also been used to remove acral pruritic nodules with some success. Interdigital recurrent folliculitis and furunculosis may also be treated with laser therapy and allowed to heal by secondary or primary closure.

Summary
In short the laser is a tool now available in veterinary medicine that allows us to provide state-of-the-art patient care. It allows procedures to be performed that could not otherwise be accomplished. It also provides a sterile, dry surgical field and improved healing, while also decreasing post surgical pain. If not used properly the patient and staff may be injured with the laser so training and experience are very important.

References
Introduction
When the dog is washed it is usual to use a detergent-based shampoo or a soap. Shampoos are preferred to soaps because the liquid shampoos are easy-to-use and provide a more workable lather. Such handling characteristics are important to ensure compliance with use instructions.

Veterinarians sell shampoos over-the-counter for general dog washing. Some shampoos include putatively active ingredients and some shampoos may have labelled indications. If they have labelled indications, shampoos have been approved by the regulator indicating that they have been examined for efficacy and safety with respect to the labelled indication and the target species.

However, shampoos are cocktails comprising a variety of ingredients, each of which has particular action. This presentation will introduce the usual constituents of commercial shampoos and described the purpose of their inclusion.

The purpose of shampoos
Shampoos which do not include active ingredients are used to cleanse the hair, fur and skin of the pet. Clean pets interact with humans better, especially where odour and dirt is disliked. Since the human-animal bond depends on interaction, it is expected that clean pets will establish a better bond with their owners in modern western societies. Animal petting is healthy for humans and guidelines require that pets must be clean to enter hospitals.

A well formulated shampoo may also improve the tactile feel of the hair, enabling combing and brushing, enabling grooming (an important part of the human animal bond for some breeds), providing greater lustre, minimising the generation of static electricity and providing a pleasant odour for the human handler.

Use of shampoos in the topical treatment of allergic and infectious skin diseases has been reviewed. While there is thought to be some benefit from the application of medicated shampoos, there is little high quality evidence for efficacy of shampoos. However, shampoos have been tested and found to be superior versus water-alone in whirlpool treatment of pruritis in dogs.

Washing dogs has been a recommendation for households where humans have respiratory allergy to dog dander. Under these conditions there is evidence to suggest that use of shampoos is not is not better than washing with water alone.

The composition of shampoos
The aims of the formulation chemist when preparing a shampoo formulation include that the shampoo
1. includes suitable surfactants and other active ingredients to ensure its cleaning function,
2. is pleasant in tactile feel, colour and fragrance,
3. has a suitable viscosity to ensure that it is pourable,
4. preferably is homogeneous and therefore does not require shaking before use,
5. should not be irritant,
6. be both chemically and physically stable: for the duration of its shelf life its colour, viscosity, smell and pH must each remain within allowable limits and each ingredient must not degrade.

Because of these requirements shampoos are normally formulated as true solutions or as isotropic colloidal solutions. Ideally, most of the constituents must be miscible with water so that when the shampoo is delivered during use the constituents do not precipitate.

Some complex shampoos include conditioning agents to improve grooming characteristics of the cleansed hair. These constituents which are purposed to conditioning their hair shaft after cleansing may be deliberately immiscible and
precipitate upon dilution with water. If the shampoo formulation includes suspended materials, then to prevent them settling before use the viscosity is adjusted, preferably to at least 500 cP.

**Anionic detergents**

Anionic detergents in shampoos are the primary ingredient which aid in cleaning. These detergents contain a fatty alkyl chain group generally from 12 to 21 carbon atoms long. The carbon chain may be saturated or unsaturated. At one end of the carbon chain is a charged polar ‘head’ which is usually a sulphonated or sulphated succinate, often using sodium, magnesium or ammonium as the counter-ion.

Anionic detergents that are frequently used in formulation of shampoos include sodium laurel sulphate, ammonium laurel sulphosuccinate, sodium dodecyl benzene sulphonate. Laurel sulphates are the most common.²³

When added to water the polar head of the detergent molecule interacts with the bipolar aqueous environment, but the fatty alkyl chain is repelled by the water. Therefore, when only a small amount of detergent is added to water, the detergent molecules disperse around the surface of the water. With this configuration the detergent does not markedly alter the solubility in water of fats, fatty acids and other oils, resulting in little cleansing ability. Further, at these low concentrations to detergent is inclined to adhere to solid objects such as hair and skin, and can result in irritancy.

As more detergent is added to the water point is reached where there is no more room at the water's surface for further molecules and additional detergent molecules must move into and interact with the aqueous environment. This interaction is possible because of the polar head, but the apolar tails are hydrophobic and are not “happy” in the aqueous phase. A curious event occurs: for each detergent there is a particular concentration at which sufficient detergent is dissolved in the water to enable chance interactions of detergent molecules with each other. The hydrophobic tails attract each other and align together, with their polar heads facing outwards to the water. This process of self assembly results in the formation of micelles and in a marked change in viscosity.² The minimum concentration for the formation of micelles is called the critical micellar concentration, or CMC, and is temperature and solution-dependent. The size and shapes of micelles varies but their longest dimension is usually less than approximately 20 nm when the micellar solution is of detergent in water alone.

For a shampoo to work, to remove the fats and oils from an animal's coat, the anionic detergent should be applied mixed with water at a concentration which exceeds the CMC. The micellar solution of detergent in water is then able to provide an environment in which fats and oils which are immiscible in water can dissolve. With the energy of scrubbing, fats and oils from the coat of the animal are moved into suspension in the water and then because of their lipophilic nature they rapidly move to the interior of the micelles; they are dissolved in the fatty environment of the micellar core. The detergent polar heads maintain an orientation toward the water, holding the micelle in aqueous solution. The result is a clear solution of oils and detergent in water. As more and more oil is dissolved into the micelles the size of the micelles increases. When the size of the micelles is sufficiently large to scatter light (> approx. 40 nm), the mixture has moved from being an isotropic solution to being a micro emulsion, or as micelles grow even further ultimately the mixture becomes a kinetically unstable emulsion with droplet sizes in the micro-metre range. At some point along this continuum the fat droplets coalesce and the surfactant action of the detergent is lost. This chemistry illustrates that dirtier dogs require more detergent micelles to enhance cleaning. An understanding of this chemistry also helps to realise that multiple short washes with an anionic detergent-containing shampoo are more efficient at cleansing than simply adding more and more detergent to an already wet dirty dog.

An animated illustration of this process can be accessed at [http://www.youtube.com/watch?v=cdKlyofu0Xw](http://www.youtube.com/watch?v=cdKlyofu0Xw).

**Cationic detergents**

Cationic detergents are sometimes included in formulations to improve grooming characteristics of clean hair. Hair generally is negatively charged and therefore anionic grooming agents will not adhere to the surface of the hair. Cationic detergents (and some polymers) are included in shampoo formulations so as to stick to and coat the hair, smoothing its surface to provide a better feel. Some examples include dimethyl diallyl ammonium chloride homopolymer, hydroxypropyltrimonium chloride. Cationic detergents can precipitate in the presence of anionic detergents, so the art of these formulations is to correctly adjust the concentration ratios to avoid physical instability.²

**Insoluble and non-ionic components**

Because water is a polar environment, most non-ionic components are insoluble. Non-ionic components such as silicones, resins, oils and waxes can be included in shampoos as grooming agents. These components precipitate from the formulation when diluted with water and then they adhere to hair, remaining behind on the coat after rinsing. These oils such as lanolin, castor oil, linseed oil, coconut oil and light paraffin oil can be used as grooming agents.
Some methylated silicones and low molecular weight oils are volatile and therefore remain on the hair for only a limited period after use. These are preferred grooming aids because they lubricate the hair for a period of time needed for grooming and then evaporate. Shampoos with these additives are best used immediately preceding grooming.

**Polymers and Saccharides**

Polymers are used as thickening agents. Well-known examples include Methocell, polyvinylalcohol, ethyl alcohol and carboxymethylcellulose. Carboxy methylcellulose is a gum with low miscibility with water. As the concentration rises to approximately 2% the formulation becomes un-pourable.

Inclusion of saccharides in a shampoo can help to improve the quality of foam, and can help to stabilise suspended conditioning particles through modification of the formulation viscosity. Saccharides which can be used include mono- and disaccharides such as glucose and fructose, or polysaccharides such as maltitriol. Longer chain saccharides are required in lower concentrations to achieve the same change to viscosity. However the longer the sugar chain becomes the less miscible with water is the moiety. Therefore, different shampoos can contain a range of different sugars each of which may be at a different concentration. Indeed, to minimise manufacturing costs it is usual to include mixes of saccharides, because separating saccharides is technically difficult and expensive.

Hydrogenated sugars lack reducing groups and therefore are preferred to non-hydrogenated sugars, because they are less susceptible to microbial fermentation or degradation by light and therefore allow for better stability of colour and smell.\(^2\)\(^,\)\(^3\)

**Co-solvents**

In order to present a homogeneous formulation despite including polymers, insoluble and non-ionic components and cationic detergents that can each result in poor water solubility of some ingredients, sometimes co-solvents are required. Typical co-solvents include alcohols such as ethyl alcohol, but also propylene glycol or glycerine can be used. These co-solvents can be irritating to skin.\(^2\)

**Preservatives, Buffers, Colour and Perfume**

Some formulations can be prone to colour changes as a result of inclusion of reducing sugars. Antioxidants and sulphites or bisulphites can be included as low concentrations to avoid unnecessarily short shelf life.

Much is made of the formulation pH in marketing of shampoos, but in reality the primary need to manage formulation pH is to achieve chemical stability and sufficient shelf life for the product. These products are diluted with copious amounts of water when in use, so the final pH of the application varies according to water quality and quantity. Suitable benign buffers, e.g., citrate, are chosen based on the pH range for which they are active.

Commercial food dyes and perfumes are often included to alter the presentation of the shampoo. Aldehydes ketones alcohols and esters of small molecular weight organic molecules are frequently used. It has been established that the choice of perfume is important, since humans are influenced in their appreciation of the feel of hair by the fragrance of the hair.\(^8\)

To prevent bacterial or fungal growth in the formulation, small quantities of antibacterial agents are often included in the formulation. Antibacterial agents used include; EDTA, formaldehyde, glutaraldehyde, benzyl alcohol, methyl paraben and imidazolidinyl urea. Care must be taken not to confuse the purpose of these agents with higher concentrations of antibacterial agents that are intended as active ingredients after dilution on an animal.\(^2\)\(^,\)\(^3\)

**Conclusion and clinical relevance**

In folk-law there are still those who teach that dogs should not be washed and those that teach the need for frequent bathing to ensure health. There is little scientific evidence for either of these positions.

Proverbially, cleanliness is next to godliness. Pragmatically, pet owners often want to clean their dogs to allow more pleasant interaction in the home, at play, and for the working dog in its workplace. Therefore, veterinarians should understand what is in a shampoo, how it functions and how it is best used to avoid causing irritation.

Older shampoo formulations are merely mixtures of an anionic surfactant and colouring and fragrance agents. Modern multi-component shampoos aim to ensure that hair is both clean and covered with a polymer film to maintain luster and to ease grooming.
References


Pododermatitis etiology
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Animal Dermatology Clinic of San Diego

Introduction
Pododermatitis is a common problem in the dog and is less common in the cat. The term pododermatitis refers to an inflammatory skin disease that affects the paws. It is a pattern of distribution not an etiologic diagnosis. The paw has many different structures (haired skin, skin folds, claw folds, claws, haired to paw pad junctional skin, and paw pads); the distribution of the disease on the paw helps to determine which differential diagnoses are more or less likely. In order to have the best clinical response to therapy it is important to have not only an accurate diagnosis, but also to understand that with chronic disease, chronic pathologic change to the tissue may occur. This change can and often does hinder therapeutic success.

Pathogenesis
Another complicating factor in determining the underlying etiology of pododermatitis in the dog is the large range of diseases that cause pedal disease. The pathogenesis of pododermatitis can be evaluated in the following way which can help improve therapeutic success. Look for predisposing factors, primary factors, secondary factors, and perpetuating factors. Failure to address any of these factors will lead to recurrence of disease or failure of therapy.

Predisposing Factors
Predisposing factors are those historical or physical findings that make the patient more susceptible or likely to develop certain conditions, in this case pododermatitis. These factors work in conjunction with either primary causes or combine with secondary causes to cause a patient to be more susceptible to clinical disease. Examples of predisposing factors here would include the following; environmental factors, like rough terrain or plant burrs; patient care, such as lack of grooming with overgrown claws or interdigital hair mats. Over grooming such as clipper burns may also cause inflammation; and patient factors including abnormal weight bearing or obesity causing abnormal weight distribution to the paws.

Primary Factors
Primary factors are the diseases or agents that directly induce the problem. The primary etiology may without any additional factors cause disease. However, once pododermatitis is present secondary and perpetuating factors occur and many times they become the focus of therapy. As with any medical problem, the primary factors can be broken down into multiple sub-groupings; Infectious, Immune mediated, Keratinization, Environmental, Congenital, Neoplastic, Metabolic, and Nutritional. The approach to defining the primary factor is similar to any medicine case. Historical evaluation and physical examination help rank the primary factors as more or less likely. The clinician should then base the diagnostic approach on what he or she feels are the most likely differentials. Many clinicians will follow flow-charts and although they are helpful, they may not take into consideration cost effectiveness of the test being recommended. Some primary causes of pododermatitis are very inexpensive yet very important to rule-out before performing more expensive diagnostic tests. An example of this is ruling out demodicosis prior to allergy testing.

The following is a list of many primary factors causing pododermatitis:

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Bacterial</th>
<th>Fungal</th>
<th>Parasitic</th>
<th>Viral</th>
<th>Immune Mediated</th>
<th>Allergic</th>
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<tr>
<td>Bacterial</td>
<td>Staph. Intermedius</td>
<td>Malassezia</td>
<td>Demodicosis</td>
<td>Papilloma virus</td>
<td>Cowpoxvirus (cats)</td>
<td>Gram negative or mixed infection</td>
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<td></td>
<td>Anaerobic infections</td>
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<td>Hookworm dermatitis</td>
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<td>Dermatophytes</td>
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<td>Deep mycoses</td>
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Secondary Factors
Secondary factors contribute to or cause disease only in the abnormal paw or in association with predisposing factors. Microorganisms act as opportunists and significantly contribute to the inflammation and pathology in the compromised pedal skin. The more commonly isolated bacterial organisms include *Staphylococcus pseudintermedius*, *Pseudomonas spp.*, *Proteus spp.*, *Escherichia coli*, and *Klebsiella spp.*. *Malassezia pachydermatis* is the most common yeast contributing to pododermatitis. It is a budding yeast that has a peanut shape. The problem here is the focus of treatment becomes the infection and the primary etiology or perpetuating factors are not addressed. When this occurs more resistant bacterial infections may occur. During consultation a frequent question asked is “which antibiotic will best treat this infection?” Perhaps a better question would be “how can this case be better diagnosed or managed?” Changing courses of antibiotics will likely yield more multi-drug resistant microorganisms. The other problem once the occurrence of secondary infection is present is the change in symptoms perceived by the owner. An originally non-pruritic pododermatitis may now be a very pruritic.

Perpetuating Factors
Perpetuating factors occur because of alterations in the normal structure and physiology of the paw as a result of predisposing, primary and secondary causes. Perpetuating factors often prevent the resolution of pododermatitis even when the primary factors are controlled. Pathologic responses are very common with chronic pododermatitis and can lead to permanent changes in the anatomy leading to persistence of the disease. Inflammation in the skin stimulates epidermal hyperkeratosis and acanthosis, dermal fibrosis, edema, glandular hyperplasia/dilation and in some cases folliculitis and furunculosis. The tissue swelling that occurs leads to deep folds and fibrotic nodules in the interdigital tissues. These folds also act as sites for the perpetuation and protection of secondary microorganisms. Regardless of the initial disease process the clinician is now faced with treating a deep fold dermatitis. These folds and swelling then cause abnormal weight bearing. The pet no longer walks on the pads but starts to walk on the haired interdigital skin causing further folliculitis and furunculosis, swelling and fibrosis to occur.

Determining the Etiology of Pododermatitis
The history obtained should focus on identifying not only primary and secondary factors but also predisposing factors and perpetuating factors. Determine if the problem is a new problem or a recurrent problem and if it is a recurrent problem, how long does it take to recur once therapy is completed. Determine the age of onset of the disease and what
the symptoms of the problem were initially. Ask if disease has been a seasonal problem and if the pet licks or scratches other locations. Find out in what type of environment the pet is kept. Determine what previous therapy has been used and if it was effective completely or partially.

Physical evaluation of the patient with pododermatitis should determine multiple clues to the underlying etiology. First assess the conformation of the paw. Is normal weight distribution present? The anatomy of the paw is complex. Determine the distribution of the disease on the paws including how many paws are diseased. The claws, claw folds, pads, and dorsal and ventral interdigital areas should be evaluated. Evaluate the paws for erythema, swelling, comedones, follicular casts, scaling, ulceration, crusting, hemorrhagic furuncles, proliferative growths and/or discharge. If discharge is present, quantify and qualify the type present. Palpate the tissue to evaluate for painfullness, and fibrosis or deep nodules. Scared, nodular lesions warrant a more guarded prognosis. Chronic interdigital nodular tissue may not return to normal and may be difficult to successfully manage with medical therapy alone.

A thorough physical examination is very important as many primary diseases have certain primary cutaneous lesions associated with them. This allows the clinician to develop his or her own flow chart as to what primary etiology is most likely, as well as save the client and patient unwarranted diagnostics or trial therapy. For example, erythema of the paws with normal anatomy, no other primary or secondary lesions and a history of pruritus in multiple paws is strongly suggestive of atopy or food allergy; In a 4 month old dog, erythema and comedones are strongly suggestive of demodex. The finding of pustules on the foot pads of a cat is almost pathognomonic for pemphigus foliaceus and warrants a biopsy. Crusting at the margins of the footpads and perioral areas is suspect for zinc responsive dermatosis or hepatocutaneous syndrome. Other findings are much less specific, such as interdigital hemorrhagic bulla, which may be due to multiple primary causes.

**Diagnostic Tests**

Which diagnostic tests should be performed is quite variable and more aggressive versus more conservative approaches are wanted depending on the clients. When infectious organisms are suspected cytologic examination is recommended. Cytologic examination does not usually establish the primary diagnosis, but is valuable in determining the type of secondary inflammation and/or infection present. Cytology allows evaluation of the cellular make-up of the discharge such as the degree of wax, lipids, keratin, neutrophils, or acantholytic cells present. When biopsies are obtained after infection has been treated, if organisms are found on cytology. When biopsies are obtained while infection is present, it can be more difficult for the pathologist to commit to a definitive diagnosis due to the background inflammation. The history must be used together with the clinical signs to determine the suspected diagnosis indicates the need for biopsies. If the primary suspicion is that the patient has an allergy, biopsy results may support that diagnosis, but the money for the biopsy may have been spent on allergy testing instead. However, if a 10 year old dog is licking and biting its paws and it never has before had those symptoms before and infections and demodicosis has been ruled out, biopsies would be recommended. Concerns about autoimmune diseases, keratinization defects, and neoplasia all require biopsy with histopathology.

Obviously many other tests may be needed to make a definitive diagnosis of the primary etiology. Which tests are most cost effective and indicated will depend on the history and complete physical examination findings. When the findings are compatible with allergy, allergy testing and/or diet trials may be indicated. If the findings are compatible with seborrhea or other keratinization defects, biopsies may be indicated. If hormonal or metabolic concerns are present blood panels and hormone level testing may be indicated.
Therapy

Prior to recommending therapy, it is important to discuss with the client the multiple potential causes of their pet's symptoms. This should include a discussion about the perpetuating problems that the clinician perceives and the more guarded prognosis when chronic proliferative changes are present. Then discuss which diseases are most likely and what the most helpful diagnostics will be to determine the main cause of disease. This is most important when the pet has chronic or recurrent disease. If there is concern about disease that will require longer term maintenance therapy, it is important at this point to explain to the owner your suspicions about why the pet is having recurrent problems and if you are correct, what long term maintenance may be required to control the pet's problems. Discuss with the client that most infections are secondary and will recur unless the primary disease is addressed. Doing this may help prevent some client from changing veterinarians multiple times looking for a "cure".

Next is to treat any secondary problems like bacterial and yeast infections. If coccoid shaped bacteria are mainly seen on cytology a good initial antibiotic selection would include Cephalexin 22mg/kg BID, Primor 44mg/kg on day one then 22mg/kg daily, or Clavamox 22mg/kg BID. If both coccoid and rod shaped bacteria are found on cytology again Primor 44mg/kg on day one then 22mg/kg or enrofloxacin at 5-10mg/kg daily or marbofloxacin at 3-5.5mg/kg daily can be started pending culture results. If Malassezia is present then topical antifungal therapy is indicated. If the infection is more severe or refractory to therapy then ketoconazole 5-10 mg/kg daily is usually effective. The length of therapy depends on the response to therapy, the occurrence of super infections, and the deep microabscesses and fibrosis present. At this point in time starting steroids is usually contraindicated. Using both antibiotics and steroids together initially makes evaluating the response to antibiotics much more difficult. Also if additional diagnostics are required, such as allergy testing, thyroid evaluation or biopsies, steroids may influence the results of those tests.

If the history and clinical signs are compatible with atopic dermatitis or food allergy consider having allergy testing done or starting an elimination diet for 8 weeks. Please realize that blood allergy tests may have false positive results and should not be used to diagnose atopic dermatitis but to select allergens for immunotherapy. It is also important if an elimination diet is recommended that the owner understand nothing else except the specialty diet is to pass the pet’s lips other than water for a period of 8 weeks. If medications are being used as an antibiotic or flea control during the diet trial this includes not dispensing the chewable form.

When chronic perpetuating factors prevent continued improvement or continue to cause relapses then surgical removal of interdigital nodules or deep interdigital folds may become necessary. This procedure is called podoplasty. A complete podoplasty involves removing all of the interdigital skin dorsally and all the haired skin ventrally on the paw. This is a tedious surgery, but very doable. For some patients there is a marked improvement in the quality of life and marked decrease in recurrent disease. Potential complications can include fissures at the junction of the central pad and digital pads ventrally.

Summary

In conclusion, pododermatitis has many causes and complicating factors which may occur. This requires a diagnostic and therapeutic approach which allows treatment of not only the primary etiology but also addresses secondary factors and predisposing and perpetuating factors. It is important to have good client communication and multiple evaluations to evaluate response to therapy.
Introduction

H1 antihistamines (AH1), more accurately referred to as ‘inverse agonists’ as they bind to and stabilise the inactive form of the H1 receptor, are used to diminish histamine mediated allergic responses associated with activation of histamine H1 receptors. They have been commonly recommended for therapeutic use in canine atopic dermatitis (CAD) despite generally poor evidence for efficacy. Review of the literature suggests there may be pharmacological reasons limiting the potential benefits of AH1s in the treatment of CAD. This presentation aims to focus on oral AH1s currently available in Australia, their pharmacokinetics and mechanisms of action, and clinical use dogs, primarily with respect to atopic dermatitis. Other veterinary species (including cats and horses), antihistamines currently unavailable in Australia, other histamine receptor antagonists and drugs with antihistamine activity (including tricyclic antidepressants) are beyond the scope of this presentation.

Part 1: Pharmacokinetics / Pharmacodynamics in Dogs

For any oral therapeutic to be effective it needs to be given at dose which achieves adequate plasma concentrations, and subsequently diffuse or be transported to target tissues where there is enough free drug to bind to the molecular target(s) with appropriate avidity and garner effects therapeutically relevant to the disease being treated. With respect to AH1, because there are no studies examining receptor occupancy and free drug concentrations in the skin (in humans these can correlate better with clinical efficacy), there is only clinical suppression of histamine wheal and flare reactions (which have limitations with respect to extrapolation of clinical efficacy) and pharmacokinetic parameters surrounding plasma concentration to assess whether the pharmacokinetics of AH1 drugs are appropriate or not in dogs. This is far from ideal, but they represent the only measurable parameters currently available.

Awareness of poor AH1 pharmacokinetics in the dog as a potential issue was popularised in Hansson et al (2004) where it was demonstrated the first generation AH1 clemastine had a very poor oral bioavailability compared with humans, and even when dosed at the upper end of recommended oral dose rates (0.5mg/kg q12) was unable to cause wheal suppression to intradermally injected histamine despite achieving comparable peak plasma concentrations (though only about 60% of the AUC) to humans. In contrast 0.1mg/kg IV achieved a much higher plasma concentration and 7 hours of histamine wheal suppression. Higher plasma protein binding (leaving little free drug) and the higher pH of dog skin (leading to less accumulation of the drug there) were pinpointed as possible causes for the problems. The data showed that most dosage regimens (0.05’0.1mg/kg q12 PO) suggested in the literature for the oral administration of clemastine to dogs were likely to give too low a systemic exposure of the drug to allow effective therapy and likely >1 mg/kg q12h would be required.

While clemastine is no longer available in Australia the point remains: we cannot assume pharmacokinetics and pharmacodynamics of AH1 in humans and dogs are the same, and we cannot assume anecdotal doses are clinically relevant.

Alkylamines: Pheniramine, Chlorpheniramine and Dextrchlorpheniramine

Pheniramine

Pheniramine (Avil®, Sanofi-Aventis Australia Pty Ltd) is a weak first generation antihistamine. No dosing guidelines for dogs were found by the author. A toxicological study was conducted in dogs though because of toxicity (primarily CNS, with severe cases showing tachycardia, hypotension, hyperthermia and uncommonly death) reported in children taking the medication and being overdosed. In 6 dogs 20mg/kg was administered with a Cmax of 2780ng/ml after one hour and an approximate t1/2 of 2.2-3.2h. Toxicity was predicted at 10000ng/ml and no dogs showed any signs of problems during the course of the study. One study found pheniramine both shorter acting and less potent than promethazine when given IV in dogs. There seems little clinical indication for use of this drug.
**Chlorpheniramine**

Chlorpheniramine (Iramine®, Mavlab Pty Ltd) is a first generation antihistamine created by halogenation of pheniramine, resulting in approximately 20x increase in potency. It is the only antihistamine registered for use in dogs in Australia. Doses recommended for treatment of allergic dermatitis in dogs range from 0.2-2 mg/kg q8-12h. The registered dose rate is “2-8 mg chlorpheniramine maleate or 1 tablet for dogs less than 10kg, 1½ tablets for dogs 10-25kg and 2 tablets for dogs greater than 25kg given every 8 to 12 hours.” This is equivalent to approximately 0.16-1 mg/kg q8-12h.

However, pharmacokinetic data in dogs from the 1970s showed a $t_{1/2}$ of only 1.6-3 hours with either IV or oral dosing, with a bioavailability of 9.4% at 2.3-3.5 mg/kg, and 35.7-39.4% at 4.5-14.2 mg/kg. A saturable first pass effect was proposed. Later studies showed a higher mean absolute bioavailability of 28.8% with high variability (SD 12.3%) but a similar $t_{1/2}$. In humans bioavailability is reported 25-50% with a $t_{1/2}$ of 2-43h. A duration of action of 4-6 hours is reported and is shorter than would be predicted from pharmacokinetic parameters.

These poor pharmacokinetics in dogs are reflected in limited intradermal histamine wheal inhibition. At oral doses of 0.46-0.62 mg/kg maximum wheal inhibition was <10% returning to baseline in 5 hours. Even at doses up to 2.5 mg/kg maximum wheal inhibition was just over 20% though some effect persisted to 8 hours. Two doses of 1.6mg/kg four hours apart showed peak inhibition of about 13% returning to baseline near 10 hours post dosing.

Clinical studies showing efficacy in dogs in other allergic models have used doses much higher than that recommended in the veterinary dermatology literature including 10 mg/kg PO in two nasal congestion models triggered by ragweed or compound 48/80. Collectively this data suggests that oral chlorpheniramine, at recommended veterinary doses unlikely to achieve adequate systemic exposure to achieve a satisfactory therapeutic outcome in a majority of canine patients. This may also explain the relative lack of frequency of side effects noted with this medication. The wide interindividual variation in pharmacokinetics, which is more common in drugs with a low bioavailability, may explain why the occasional dog anecdotally shows either improvement and / or side effects at currently recommended doses.

**Dexchlorpheniramine**

Dexchlorpheniramine (Polaramine®, Merck Sharp & Dohme), is the d’isomer (and primary active isomer) of the racemic compound chlorpheniramine, and is twice as active as chlorpheniramine by weight. The absorption, distribution, metabolism and elimination of dexchlorpheniramine have not been specifically described in any species but it is thought the pharmacokinetics of dexchlorpheniramine are likely to be similar to that of chlorpheniramine. Dosing recommendations for dogs were not found, but would likely be approximately half of the equivalent dose of chlorpheniramine where the 2mg immediate release tablets were used. The effect of the 6mg slow release ‘repetab’ in dogs is unpredictable since several slow release formulations of chlorpheniramine in one canine study had less favourable pharmacokinetics than the immediate release formulation.

**Ethanolamines: Diphenhydramine**

Diphenhydramine is a first generation antihistamine. Doses of 1-4 mg/kg q8h have been recommended. A single pharmacokinetic study in dogs following dosing approximately 2.16mg/kg diphenhydramine (as diphenhydrinate) PO found a $C_{max}$ of 1501 ng/ml at $T_{max}$ 3.2h with an AUC of 9500ng.h/ml and $t_{1/2}$ of 4.4h. This contrasts markedly with a recent study showing a significant first pass metabolism with much poorer pharmacokinetic figures following 1mg/kg PO of $C_{max}$ 2.6-3.3ng/ml at $T_{max}$ 1-2h with an AUC of 12.7-17.4ng.h/ml and $t_{1/2}$ of 4.2-6.6h. With human pharmacokinetic parameters between these extremes, and with diphenhydramine concentrating in the skin significantly less than fexofenadine and causing significantly less histamine wheal and flare suppression than fexofenadine it is hard to make recommendations regarding dosing in dogs aside from the likely appropriateness of q8h hour dosing.

**Phenothiazines: Promethazine**

Promethazine (Phenergan®, Sanofi-Aventis Australia Pty Ltd) is a first generation antihistamine. Suggested doses for allergic dermatitis in dogs range from 1-2.5 mg/kg q12h. A pharmacokinetic study showed poor oral bioavailability
compared with IV or IM administration. Following dosing of 3.1mg/kg promethazine PO, a Cmax of 10.8 ng/ml at Tmax 2h with an apparent t1/2 of 8.5-27.7h (data limited more accurate calculations). This suggests that canine doses likely need to be increased to match human pharmacokinetics. However, as with chlorpheniramine, the availability of poorly absorbed drugs is likely to be more variable, and more easily influenced by other factors, than that of efficiently absorbed compounds meaning occasional successes at doses lower than those expected to be therapeutic may be seen.

**Piperazines: Hydroxyzine, Cetirizine & Levocetirizine**

**Hydroxyzine**
Hydroxyzine is a first generation antihistamine historically recommended for use 2-7 mg/kg q8h though more recent pharmacokinetic and pharmacodynamic studies based on histamine inhibition supported a maximal antihistamine effect of 2mg/kg q12h though >50% wheal suppression was achieved for 18-24 hours after a single dose. Systemic availability of hydroxyzine is 72% (similar to humans) and it is rapidly converted to the active metabolite cetirizine with an AUC 10x that of hydroxyzine. No significant first-pass effect was noted. Chronic administration of hydroxyzine does not significantly alter the pharmacokinetics.

**Cetirizine**
The pharmacokinetics of orally administered cetirizine have not been fully elucidated in the dog but the pharmacokinetic-pharmacodynamic studies of hydroxyzine would strongly support that cetirizine also needs to be dosed twice daily in the dog for maximum effect. The ideal oral dose remains unknown (0.5-1 mg/kg q24h has been suggested) though 1mg/kg q12 would seem a reasonable estimate given approximately 45% of the oral dose of hydroxyzine in humans is converted to cetirizine. This is supported by a study where 0.6 mg/kg cetirizine was dosed showed a 2h Cmax of 0.99-1.67 µg/ml which was less than the mean Cmax (2.41µg/ml) of cetirizine following hydroxyzine dosing at 2mg/kg. In contrast to this is the persistent suppression of wheal and flare to D. farinae antigen (50% suppression) or histamine (29.2% suppression) 7 days after a 7 day course dosed at 1 mg/kg q24h. Cetirazine is a P-glycoprotein substrate (P-gp) and showed up to an 8.7x increase in the brain of P-gp deficient mice compared with controls. However, this was still only ~5% of the brain penetration of hydroxyzine. Mild sedation may be seen if concurrently dosed with P-gp inhibitors.

**Levocetirizine**
Levocetirizine (Xyzal®, UCB Pharma) is the R-enantiomer of racemic cetirizine. It is the most pharmacologically active enantiomer and displays approximately 30-fold higher affinity to human H1 receptors compared with dextrocetirizine. In humans and probably dogs, the clearance of levocetirizine is slower than dextrocetirizine. In humans following a 5mg recommended dose there is a Cmax of 270 ng/ml with an AUC of 2310 ng.hr/ml and t1/2 of 7.7h. Despite this short half life once daily dosing is effective, and this may be explained by its slow dissociation rate from the H1 receptor, and relatively high unbound fraction in the skin leading to high receptor occupancy. Pharmacokinetics in dogs have only been examined in one study dosing at 0.25 mg/kg (equivalent) PO and revealed Cmax 74.4 ng/ml at a Tmax of 3.6h with an AUC of 791 ng.hr/ml and t1/2 of 6.6h. Based on a recommended dose of racemic cetirizine of 1mg/kg it would seem prudent that a dose of at least 0.5mg/kg levocetirizine is appropriate. In the absence of any pharmacodynamic studies no recommendation can be made for q12h vs. q24h dosing in this species.

**Piperidines: Cyproheptadine, Loratidine & Desloratidine**

**Cyproheptadine**
Cyproheptadine (Periactin®, Aspen Pharmacare Australia Pty Ltd) is a tricyclic first generation antihistamine. Suggested doses for allergic dermatitis in dogs range from 0.1-2 mg/kg q8-12h though a dose of 0.1-0.2mg/kg/day was found completely ineffective in 16 dogs with AD in a placebo controlled study. Limited pharmacokinetic studies at 1mg/kg PO in dogs found a Cmax of 32-34 ng/ml at Tmax at 0.5h with a t1/2 of approximately 3h. This is similar to the human pharmacokinetics following an 8mg dose of Cmax 30ng/ml and t1/2 of 4h, and would support a dose of 1mg/kg q8h, higher than some doses previously recommended.

**Loratidine**
Loratidine is a second generation derivative of piperidine antihistamines. While a dose of 0.5mg/kg q24h has been suggested, no pharmacokinetic data for this antihistamine in dogs has been published.

**Desloratidine**
Desloratidine (Aerius®, Schering-Plough Pty Ltd) is the active metabolite of loratidine and is 2.5-4x more potent that the parent molecule (depending on the clinical model). Despite a higher H1 receptor affinity, longer dissociation half life and longer plasma half-life in humans it is less effective at histamine wheal inhibition than levocetirizine because of a lower unbound fraction in the skin. Clinical efficacy though is comparable in urticaria and allergic rhinitis. Approximately 6% of humans are ‘poor metabolisers’ of desloratidine with increased systemic exposure, though without an adverse affect on tolerability or safety.

In a pharmacokinetic study in dogs following a dose of 0.48-0.71 mg/kg desloratidine PO a Cmax of 393 ng/ml at Tmax 3.2h with an AUC of 6511 ng.h/ml and t½ of 11.2h was reported. While the t½ in humans is longer than dogs at 27h, at the recommended dose of 5mg the Cmax is 2.18 ng/ml and AUC 78 ng.h/ml. This suggests that, pending pharmacodynamic evidence to the contrary, while no adverse reactions were noted, substantially lower doses may be applicable in dogs. The small unscored 5mg tablet may limit the amount of practical dose reduction, though a liquid formulation 0.5mg/ml is available.

**Fexofenadine**

Fexofenadine is the active metabolite of terfenadine and is a second generation antihistamine. In the only pharmacokinetic study in dogs (which was done as part of the original toxicity studies) fexofenadine did not prolong QTc in dogs when administered at a dosage of 10 mg/kg/day orally for 5 days despite these dosages producing plasma concentrations at least 28 times greater than those seen after administration of therapeutic dosages (60mg twice daily) to humans. Fexofenadine has been used with therapeutic success in canine AD at 18mg/kg PO once daily but there was no pharmacokinetic rationale for that dose and lower doses may also be successful. As fexofenadine is a P glycoprotein substrate (as with several other AH1s) concurrent use of ketoconazole or itraconazole may increase fexofenadine concentrations and use of rifampicin may increase fexofenadine clearance. Concurrent dosing with cyclosporin did not, however, increase brain penetration. In humans, fexofenadine penetrated into and concentrated in the skin compared with plasma to a significantly greater extent than chlorpheniramine, diphenhydramine and, to a lesser extent, loratidine, and caused significantly greater suppression of wheal and flare at most time points.

**Part 2: H1 receptors**

The major tissue location of histamine H1 receptors is on smooth muscle and vascular endothelium. Histamine released from degranulated mast cells binding to these receptors is an integral part of the wheal and flare that is the hallmark of immediate hypersensitivity. While in the dog histamine is not a major direct mediator of pruritus, H1-receptors (H1R)are distributed on several cell lineages (Table 1), most of which are either targets of inflammatory damage or active components of the inflammatory cascade. H1R-mediated actions of histamine include enhanced release of histamine, proinflammatory cytokines and chemokines, up-regulation of cellular adhesion molecule expression, stimulation of granulocyte accumulation in tissues, and of antigen-presenting activity. Functional histamine receptors are expressed by human T cells and dendritic cells but H1R are not expressed on Langerhan cells. In particular, activation of the H1R in immature and mature dendritic cells increases antigen-presenting capacity, proinflammatory cytokine production, and Th1 priming activity. These actions may be relevant in the progression of allergic inflammation and in immune modulation, suggesting a potential use of H1R blockade for the control and/or prevention of chronic responses. Interestingly, whereas Th1 cells show a predominant expression of H1-receptors, Th2 cells show an increased expression of H2-receptors.

<table>
<thead>
<tr>
<th>Table 1: Histamine H1 Receptor Cellular or Tissue Location</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth muscle (airway and vascular)</td>
<td>33</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>34, 40</td>
</tr>
<tr>
<td>Bone marrow stromal cells</td>
<td>35</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>42</td>
</tr>
<tr>
<td>Keratinocytes</td>
<td>39</td>
</tr>
<tr>
<td>T-cells</td>
<td>36</td>
</tr>
<tr>
<td>B cells</td>
<td>41</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>37</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>41</td>
</tr>
<tr>
<td>Monocytes</td>
<td>41</td>
</tr>
<tr>
<td>Macrophages</td>
<td>41</td>
</tr>
<tr>
<td>Splenocytes</td>
<td>38</td>
</tr>
<tr>
<td>Sensory neurons dorsal root ganglia</td>
<td>41a</td>
</tr>
<tr>
<td>Skin specific sensory neurons</td>
<td>41a</td>
</tr>
<tr>
<td>Hepatocytes</td>
<td>41</td>
</tr>
<tr>
<td>Chondrocytes</td>
<td>41</td>
</tr>
</tbody>
</table>
Part 3: Biological Effects of Antihistamines

It is well established that oral antihistamines exert their antihistaminergic effect via inhibition of histamine H1 receptors. However, several antihistamines have also been reported to have additional H1 receptor independent anti-inflammatory effects (Table 2). Some of these receptor-independent anti-inflammatory effects have only been noted at higher concentrations of the drug than those typically achieved in a clinical context, raising questions over their clinical relevance. However, the ability of later second generation anti-histamines especially to concentrate differentially in the skin compared with plasma (e.g. fexofenadine to 41.3x, desloratidine up to 125x and levocetirizine up to 2x but with a much higher unbound fraction) has lead to the hypothesis that that the accumulation of some drugs in target tissues during chronic treatment might give rise to concentrations capable of exerting anti-allergic actions or enhancing anti-inflammatory effects. Other anti-inflammatory effects, such as down-regulation of adhesion molecules or cytokines, have been observed in vitro at concentrations close to the physiological range and have been confirmed in vivo. The anti-inflammatory effects of AH1 are likely milder than those of glucocorticoids.

The mechanisms underlying the receptor-independent inhibitory influence on the generation of cytokines and adhesion molecules are not completely known, although there is evidence highlighting the ability of AH1 to downregulate constitututive H1 receptor-dependent NF-κB activation even in the absence of histamine. It has also been suggested that high doses of some AH1 may also bind to H4 receptors.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target Cell</th>
<th>Effect (In vitro)</th>
<th>Effect In vivo</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Generation Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>Eosinophils</td>
<td>↑ apoptosis</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td>Clemastine</td>
<td>Macrophages, monocytes</td>
<td>↓ TNF-α, ↑ IL-6</td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Eosinophils</td>
<td>↑ apoptosis</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td><strong>Second Generation Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetirizine</td>
<td>Keratinocytes</td>
<td>CCL17, CD54, IL-1β, CXCL8/IL-8, NK-1R, MHCII, CCL2, RANTES/CCL5, GM-CSF, MIF, ICAM-1, sICAM-1</td>
<td>↓ VCAM-1</td>
<td>32a, 46, 49, 55, 56, 71, 77</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>ICAM-1</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Conjunctival epithelium</td>
<td>ICAM-1</td>
<td></td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Airway epithelial cells</td>
<td>GM-CSF, CXCL8/IL-8</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Dermal fibroblasts</td>
<td>CCL17, ICAM-1</td>
<td></td>
<td>46, 67</td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td>O2·</td>
<td></td>
<td>32a</td>
</tr>
<tr>
<td></td>
<td>Eosinophils</td>
<td>chemotaxis, survival</td>
<td>early but ± late phase response</td>
<td>32a, 78, 81</td>
</tr>
<tr>
<td></td>
<td>T-cells</td>
<td>INF-γ</td>
<td></td>
<td>32a</td>
</tr>
<tr>
<td></td>
<td>PBMCs</td>
<td>IL-10, INF-γ</td>
<td></td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>Basophils</td>
<td>IL-3, TNF-α, CXCL8/IL-8, IL-6</td>
<td></td>
<td>52, 76</td>
</tr>
<tr>
<td></td>
<td>Mast cells</td>
<td>IL-3, TNF-α, CXCL8/IL-8, IL-6</td>
<td></td>
<td>52, 76</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>Keratinocytes</td>
<td>CD54, CXCL8/IL-8, Th1 chemokines, MHCII, RANTES/CCL5, CXCL10, GM-CSF, ICAM-1, CCL2, CCL20</td>
<td>↓ GM-CSF, CXCL8/IL-8</td>
<td>32a, 49, 56, 66</td>
</tr>
<tr>
<td></td>
<td>Airway epithelial cells</td>
<td>GM-CSF, CXCL8/IL-8</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Nasal lavage</td>
<td>IL-4, CXCL8/IL-8</td>
<td></td>
<td>63, 69</td>
</tr>
<tr>
<td></td>
<td>Endothelial cells</td>
<td>VCAM-1, eotaxin</td>
<td></td>
<td>32a, 79</td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>E-selectin, P-selectin, T&lt;sub&gt;reg&lt;/sub&gt;</td>
<td></td>
<td>32a</td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td>O2·</td>
<td></td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Eosinophils</td>
<td>chemotaxis, TIMP-1 &amp; 4, MMP-9, EGF, IL-10, IL-7, SCF</td>
<td>in nasal lavage</td>
<td>32a, 57, 63</td>
</tr>
<tr>
<td></td>
<td>T-cells</td>
<td>GATA-3, ICAM-1</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Lymphocytes</td>
<td>ICAM-1</td>
<td></td>
<td>32a</td>
</tr>
<tr>
<td>Loratidine</td>
<td>Keratinocytes</td>
<td>Th2 chemokines, GM-CSF, CXCL8/IL-8, RANTES/CCL5, CXCL10</td>
<td>↓ VCAM-1</td>
<td>56, 62</td>
</tr>
<tr>
<td></td>
<td>Endothelial cells</td>
<td>P-selectin</td>
<td></td>
<td>32a</td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>VCAM-1</td>
<td></td>
<td>32a</td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td>O2·</td>
<td></td>
<td>32a</td>
</tr>
<tr>
<td></td>
<td>T-cells</td>
<td>IL-5</td>
<td></td>
<td>32a</td>
</tr>
</tbody>
</table>
Table 2: Key: AR = Allergic Rhinitis, BAL = Brochioalveolar Lavage Fluid, CCL = Chemokine Ligand, EGF = Heparin-Binding Epidermal Growth Factor, GM-CSF = Granulocyte-Macrophage Colony Stimulating Factor, ICAM = InterCellular Adhesion Molecule, IFN = Interferon, IL = Interleukin, LT = Leukotriene, MIF = Macrophage migration Inhibitory Factor, NF-κB = Nuclear Factor-κB, PG = Prostaglandin, PBMCs = Peripheral Blood Mononuclear Cells, PBL = Peripheral Blood Leukocytes, SCF = Stem Cell Factor, TARC = Thymus and Activation Regulated Chemokine, Th = T helper, TIMP = Tissue Inhibitor of Metalloproteases, TNF = Tumor Necrosis Factor, VCAM = Vascular Adhesion Molecule

**Part 4: Clinical Use of Antihistamines in Canine Atopic Dermatitis**

**Why even bother?**

Given the general lack of quality evidence for efficacy of antihistamines in the treatment of atopic dermatitis in dogs and humans, the question of whether they should be used at all is a reasonable one. This is further compounded by the complexity of the mechanisms of pruritus and inflammation in CAD, which AH1 cannot be expected to address
all of, and the anti-inflammatory impact of AH1s are which generally of reduced magnitude and extent compared with that of glucocorticoids. However,

- the generally poor standard of trialling means that despite over 30 years of studies in humans and dogs, there is inadequate quality evidence to actually assess efficacy. 82, 82a
- there are isolated studies of reasonable quality in humans 81 and dogs 22 that suggest there may be some efficacy and that antihistamines therapy in AD is worthwhile pursuing.
- in canine AD in particular there are serious deficiencies in our knowledge of the most appropriate antihistamines to use in this species, the correct doses to be using, when to be using them, and the length of time to be trialling them for to achieve maximal response.

This means that better designed studies examining pharmacokinetics, pharmacodynamics and clinical efficacy of antihistamines in CAD are required before we will have the answers to the big question of efficacy. What is possible though, on re-examination of the historical data presented so far, is to build a roadmap that can maximise the chance of a good clinical outcome with these therapeutics.

**Which antihistamines should be used?**

To maximise the chance of a successful outcome any antihistamines used should have satisfactory pharmacokinetics in a majority of patients. As all the first generation antihistamines in Australia, with the exception of hydroxyzine, have unfavourable pharmacokinetics in the dog, as well as, in one literature review, no more than, a 16.7% chance for satisfactory control of pruritus with any single AH1 22 it is difficult to recommend their use. A more recent open retrospective study in 171 dogs with atopic dermatitis found at least partial responses in 32% of dogs treated with chlorpheniramine 0.4-0.6mg/kg q8h, and 65.1% of dogs treated with diphenhydramine 2-2.5mg/kg q8h. The doses were both at the higher end of the recommended range. Importantly, it was noted by the authors of the study that compliance is an issue with long term q8h dosing. 89 Therefore, even with a partially positive outcome, it remains difficult to recommend these AH1s for any longer than short term therapy of canine AD.

Hydroxyzine has proven pharmacokinetics in the dog and given it is rapidly converted to cetirizine, whose active enantiomer is levocetirizine, which in turn has more favourable pharmacokinetics and pharmacological activity (at least in humans). Given recent blinded placebo-controlled studies showing some efficacy for both hydroxyzine 84 and cetirizine 85 (though not without their limitations) all these antihistamines should be considered as potentially useful.

Loratidine has been little studied in the dog and is not recommended but the pharmacokinetics of desloratidine, its major active metabolite, are very favourable. 20 Fexofenadine has also been shown in one study to be efficacious in the control of pruritus in AD, 22 and also shown to have adequate pharmacokinetics in the dog when dosed orally. 21 Both desloratidine and fexofenadine should be considered potentially useful.

**How long should antihistamines be trialled for to assess efficacy?**

While effects on immediate hypersensitivity may only take a matter of hours, if it is presumed some of the effects of AH1 on cytokines or adhesion molecules are clinically relevant it would be expected these would be significantly more slow acting, and potential benefits of these anti-inflammatory and immunomodulatory actions might be more correctly evaluable after long-term continuous treatment. 32a

In humans treated with fexofenadine for AD improvement was noted at 4 weeks with significantly more improvement at 12 weeks. 86 In a study of treatment of allergic rhinitis comparing on-demand therapy with continuous therapy with levocetirizine, improvement was similar to the 4th month but for the next 2 months was significantly better in the continuous therapy group. 80

In dogs, in the study examining fexofenadine in AD, pruritus was less at 6 weeks than 3 weeks, and CADESI was only significantly different from baseline at 6 weeks. 22 In another study examining a variety of antihistamines with concurrent essential fatty acid supplementation, further improvement in pruritus was seen in all dogs from week 8 to week 12 despite only 4 weeks on essential fatty acid therapy, 87 a period likely to be too brief to contribute significantly reduction of pruritus. 88
The previous recommendation for duration of therapy for trialling antihistamines in the treatment of canine AD was 1-2 weeks. Given the evidence above 4-6 weeks should be considered a minimum duration to adequately assess improvement in response to any of the recommended AH1.

What is the right dose of antihistamine?

The literature shows that a proportion of the anti-inflammatory effects noted in vitro and in vivo require higher concentrations than those likely to be achieved by current human dosing guidelines. Therefore, in the absence of adequate pharmacokinetic / pharmacodynamics studies for all AH1 in the dog bar hydroxyzine, aggressive dosing of AH1 is recommended (Table 3) to maximise the chance of a positive clinical outcome. This rationale further emphasises use of AH1 with likely appropriate pharmacokinetics, wide therapeutic windows and an absence of dose-limiting side effects such as sedation. Dose tapering no more rapidly than monthly is suggested if a positive clinical outcome is achieved.

<table>
<thead>
<tr>
<th>Recommended Antihistamine</th>
<th>Suggested Trial Dose</th>
<th>Suggested Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyzine</td>
<td>2mg/kg</td>
<td>q12h</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>1mg/kg</td>
<td>q12h</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>0.5-0.75mg/kg</td>
<td>q12-24h</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>10-18mg/kg/day</td>
<td>q12-24h</td>
</tr>
<tr>
<td>Desloratidine</td>
<td>0.25-0.5mg/kg</td>
<td>q24h</td>
</tr>
</tbody>
</table>

Table 3: Suggested antihistamine doses

How can antihistamines be used with other therapies?

Is there benefit from using antihistamines in combination with glucocorticoids?

Possibly. There is conflicting evidence in the few studies that have examined this. An in vitro study examining mometasone and desloratidine effects on eosinophil survival and cytokine production found additive effects on inhibition of IL-6 and IL-8 and eosinophil survival. These effects were most noticeable at low mometasone concentrations. Two in vivo human studies comparing efficacy of topical mometasone with or without concurrent cetirizine, and topical fluticasone with or without concurrent cetirizine in cases of allergic rhinitis found no additive effect from the AH1s. However, another human study comparing responses to flunisolide with or without loratadine in cases of non-allergic eosinophilic rhinitis did show a significant additive effect. These findings suggest that AH1 may have some additive effect where low doses of glucocorticoids are being administered but are less likely to be steroid sparing with administration of higher glucocorticoid doses.

Is there benefit from using antihistamines in combination with allergen specific immunotherapy?

Possibly. A single double-blinded placebo-controlled study in humans dosed levocetirizine 5mg q24h from 2 days prior to d21 of bee immunotherapy. Side effects were more frequent in the placebo group and at d120 IL-10 was significantly elevated in the levocetirizine group only. A second study in humans receiving terfenadine or placebo during rush venom immunotherapy showed after 3 years of immunotherapy 29% of sting challenged patients who received placebo had a mild to moderate systemic allergic reactions but none of the terfenadine treated patients did. AH1 during induction of venom immunotherapy may enhance efficacy of treatment and is recommended in dogs. Whether this is applicable to allergen specific immunotherapy in CAD is unknown.

Is there benefit from using antihistamines in combination with other antihistamines?

Possibly. In vitro studies primarily show that not all AH1 have the same effects on cytokines. This raises the possibility that careful combination of AH1 may have additive clinical effects. Specifically hydroxyzine / cetirizine / levocetirizine (which may affect some T_H1 cytokines) may combine well with desloratidine (which has effects on T_H2 cytokines) to try and better treat both the acute and chronic phases of AD. Fexofenadine showed effects on both T_H1 and T_H2 cytokines.

Are there other potential uses for antihistamines?

Chronic use of antihistamines may delay onset of allergies.
In a murine model of allergic airway disease, treatment with desloratidine prior to and during sensitisation suppressed allergen-induced Th2 responses, as well as development of eosinophilic airway disease, emphasising an important immune modulating function of histamine, and suggested a potential role of H1R-anagonists in preventive strategies against allergic diseases.  

In humans, two double blinded placebo controlled studies confirmed that use of cetirizine 0.25mg/kg q12h significantly reduced compared with placebo the development of asthma in infants with atopic dermatitis with an atopic parent or sibling. This effect was most sustained over the 3 years of the second study in grass pollen sensitised infants. It was considered impractical to start therapy prior to sensitisation, but use of AH1 in high risk infants (family history of AD, early sensitisation) with AD were considered the optimal target for therapeutic intervention. In light of this, use of AH1 early in the course of AD may be more useful.

On the other hand it is unlikely short term AH1 are effective for prevention of acute atopic flares in CAD. Cetirazine administered 24 and 2 hours prior and hydroxyzine 24, 12 and 2 hours prior to allergen exposure was ineffective in preventing acute atopic flare in a sensitised dog model. Topical triamcinolone spray applied 24 and 1 hours prior to allergen exposure was completely effective.

Antihistamines may be worth trialling with primary secretory otitis media.

Administration of histamine intra-arterially or topically to dogs increases perfusion pressure in the eustachian tube. This effect was able to be blocked with both intra-arterial promethazine or chlorpheniramine. Given the lack of any effective medical treatments for primary secretory otitis media in the dog and the lack of understanding of the pathogenesis, AH1 trial may be warranted in this disease if surgery is not an option.

References


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Surgical treatment of chronic pododermatitis
Mona Boord, DVM, Dip ACVD,
Animal Dermatology Clinic of San Diego

Introduction
Pododermatitis is a common problem in the dog and is less common in the cat. The term pododermatitis refers to an inflammatory skin disease that affects the paws. It is a pattern of distribution not an etiologic diagnosis. The paw has many different structures (skin, skin folds, claw folds, claws, haired skin, pad junction, and pads) and distribution of the disease on the paw helps to determine which differential diagnoses are more or less likely. In order to have the best clinical response to therapy it is important to have not only an accurate diagnosis, but also to understand that with chronic disease, chronic pathologic change to the tissue may occur. This change can and often does hinder therapeutic success.

Pathogenesis
A complicating factor in determining the underlying etiology of pododermatitis in the dog is the large range of diseases that may cause pedal disease. The pathogenesis of pododermatitis can be evaluated in the following way which can help improve therapeutic success. Look for predisposing factors, primary factors, secondary factors, and perpetuating factors. Failure to address any of these factors will lead to recurrence of disease or failure of therapy.

Perpetuating Factors
Perpetuating factors occur because of alterations in the normal structure and physiology of the paw as a result of predisposing and primary causes as well as the response to secondary infections. Perpetuating factors often prevent the resolution of pododermatitis even when the primary factors are controlled. Pathologic responses are very common with chronic pododermatitis and can lead to permanent changes in the anatomy leading to persistence of the disease. Inflammation in the skin stimulates epidermal hyperkeratosis and acanthosis, dermal fibrosis, edema, glandular hyperplasia/dilation and in some cases folliculitis and furunculosis. The resultant tissue swelling leads to deep folds and fibrotic nodules in the interdigital tissues. These folds also act as sites for the perpetuation and protection of secondary microorganisms. Regardless of the initial disease process the clinician is now faced with treating deep fold dermatitis. These folds and swelling then cause abnormal weight bearing. The pet no longer walks on the pads but starts to walk on the haired interdigital skin causing further folliculitis and furunculosis, swelling and fibrosis.

Clinical evaluation of the paw
Physical evaluation of the patient with pododermatitis should determine multiple clues to the underlying etiology. First assess the conformation of the paw. Is normal weight distribution present? The anatomy of the paw is complex. Determine the distribution of the disease on the paws including how many paws are diseased. The claws, claw folds, pads, and dorsal and ventral interdigital areas should be evaluated. Evaluate the paws for erythema, swelling, comedones, follicular casts, scaling, ulceration, crusting, hemorrhagic furuncles, proliferative growths and/or discharge. If discharge is present, quantify and qualify the type present. Palpate the tissue to evaluate for painfulness, and fibrosis or deep nodules. Scared, nodular lesions warrant a more guarded prognosis. Chronic interdigital nodular tissue may not return to normal and may be difficult to successfully manage with medical therapy alone.

Therapy
Prior to recommending therapy, it is important to discuss with the client the multiple potential causes of their pet’s symptoms. This should include a discussion about the perpetuating problems that the clinician perceives and the more guarded prognosis when chronic proliferative changes are present. Then discuss which diseases are most likely and what the most helpful diagnostics will be to determine the main cause of disease. This is most important when the pet has chronic or recurrent disease. If there is concern about disease that will require longer term maintenance therapy, it is important at this point to explain to the owner your suspicions about why the pet is having recurrent problems and if you are correct, what long term maintenance may be required to control the pet’s problems. Discuss with the client that most infections are secondary and will recur unless the primary disease is addressed. Doing this may help prevent some client from changing veterinarians multiple times looking for a “cure”.

Next is to treat any secondary problems like bacterial and yeast infections. The length of therapy depends on the response to therapy, the occurrence of super infections, and the deep microabscesses and fibrosis present. At this point in time starting steroids is usually contraindicated. Using both antibiotics and steroids together initially makes evaluating the response to antibiotics much more difficult.
If the history and clinical signs are compatible with atopic dermatitis or food allergy consider having allergy testing done or starting an elimination diet for 8 weeks. It is also important if an elimination diet is recommended that the owner understand nothing else except the specialty diet is to pass the pet's lips other than water for a period of 8 weeks.

When chronic perpetuating factors cause abnormal weight bearing and deep follicular cysts prevent continued improvement or cause recurrent cysts then surgical removal of interdigital nodules or deep interdigital folds may become necessary. This procedure is called fusion podoplasty. The first article presented in 1991 by Swaim and a newer publication in 2011 by Papazoglou, have reviewed cases and describe this surgical procedure in detail\textsuperscript{1,2}. This is a salvage procedure similar to a total ear canal ablation being a salvage procedure in chronic proliferative otitis. A complete podoplasty involves removing all of the interdigital skin medial and lateral to the digits and all the haired skin on the ventral paw. This is a tedious surgery, but can be achieved. For most patients there is a marked improvement in the quality of life and marked decrease in recurrent disease. Potential complications can include fissures at the junction of the central pad and digital pads ventrally.

A partial fusion podoplasty is an option when only part of the paw is involved in the disease process. The attempt should be to remove the scar tissue and improve the weight bearing of the patient.

**Surgical procedure**

The paw is surgically clipped and prepared with surgical scrub. A tourniquet is applied over the metacarpal or metatarsal area. The incision is started on the dorsal paw. The incision is made to remove the lateral and medial skin from the digits leaving the skin dorsally to cover the dorsal digit. On the lateral fourth digits and medial third digit enough skin must remain on the paronychia to cover the digit to allow for the second and fifth digits being shorter. Blunt dissection is used to separate the scarred tissue from the digital nerves and blood vessels. Depending on the amount of time this takes the tourniquet is released for several minutes to allow blood flow and prevent thrombi. Then the ventral interdigital haired skin is excised. The only tissue that should remain is the central and digital pad tissue. One should attempt to removal all hair follicles. The paw is then soaked in diluted chlorhexidine and flushed with saline. A ¼ inch penrose drain is placed between the central pad and digital pads. The digital pads are apposed to each other and to the central pad. The dorsal skin is then closed. The paw is bandaged in a split to prevent extension of the paw. The bandage should apply enough pressure to prevent excessive bleeding but not be so tight as to create ischemic damage. The bandage is changed in 6-12 hours. The bandage is initially changed every other day. The drain is removed in 2 days. In 10-14 days the bandage can be applied without the splint. The main side effect with this procedure is a separation of the digital and central pads. This will then heal by secondary intention. In one study evaluating 7 dogs one developed necrotized fascitis. A variation on the partial fusion podoplasty has been published for dogs with abnormal weight bearing which has created thickened scar tissue on the medial aspects of the fifth digits and deep interdigital cysts. In this surgery the CO2 laser is used to ablate the abnormal tissue and the skin is allowed to heal by second intention\textsuperscript{3}

**References**:

Pemphigus Foliaceus
Mona Boord, DVM, DipACVD,
Animal Dermatology Clinic of San Diego

Objectives
Pemphigus foliaceous (PF) is one of the more common autoimmune skin diseases presented to veterinary dermatologists. This lecture will focus on assisting the veterinarian to recognize the variable clinical presentations, determine the best site selection for biopsy and emphasize the various medical therapies available to treat this complicated disease.

Introduction
The group of diseases under the name pemphigus are blistering, intraepidermal skin diseases. The blisters occur due to auto-antibody binding to cellular adhesion desmosomal molecules. Some of these molecules are calcium dependent transmembrane glycoproteins. Binding of auto-antibody to the molecule results in an activation of intracellular pathways resulting in loss of cellular adhesion and acantholysis. In humans, pemphigus foliaceous is an autoimmune skin disease triggered by auto-antibody binding to desmosomal cadherin, desmoglein 1 (Dsg1), yet this glycoprotein is recognized by auto-antibodies in fewer than 10% of dogs clinically and histopathologically diagnosed with pemphigus foliaceous. Further work is being performed to better identify the more common molecules in the dog. Most prevalence reports were done in the mid-1980s after the first published cases in 1977. The prevalence at the Animal Dermatology Clinics is 2%.

Clinical disease signalment and signs
There appears to be a genetic factor that may predispose to canine PF. Studies from different regions of the world have different breeds that exhibit a higher odds ratio to develop PF. In the various reports Akitas, bearded collies, Newfoundland, Schipperke, Doberman, Chows, Shar-peis are mentioned with Chows and Akitas at the top of many lists. Ultra-violet light is an experimental trigger factor for this disease and investigators have reported worsening of symptoms in the summer months. There are many reports of drug induced pemphigus foliaceus in humans and several anecdotal reports in our canine patients. The best review of drug induced pemphigus foliaceus disease in dogs is secondary to a Metaflumizone/amitraz combination product for topical use in the dog.

The clinical presentation varies from focal involvement to whole body disease. The lesions may include pustules, thick adherent crusts, erosions, ulcers, scale and alopecia. For many dermatologic diseases there is a typical distribution of lesions that will be seen that help the clinician determine the primary disease. However the distribution of lesions with pemphigus foliaceous can quite be variable. Some cases will remain localized to the head and face, yet others cases have a generalized distribution and still others may have severe foot pad involvement as the only clinical sign. Pruritus is variable as well and seems to be more common in the generalized form. Some patients present with systemic symptoms of lethargy, anorexia, weight loss and fever. Systemic signs are usually only noted with widespread lesions. Feline PF lesions are similar but finding pustules of the cat is very rare. Facial lesions with erosions and yellow crusts including the ears are common. These lesions are usually bilateral and symmetrical. The paws may be involved with pustules and caseated debris in the claw folds.

Diagnostics
When the differential diagnosis of pemphigus exists, cytology is a quick in house diagnostic test that may demonstrate acantholytic keratinocytes. These acantholytic cells are keratinocytes with a rounded morphology that may be seen as single cells or in rafts. These cells will be seen mixed with nondegenerated neutrophils and one may see eosinophils. There are diseases that can trigger acantholysis of keratinocytes such as Trichophyton hyphae through proteases and Staphylococcus hyicus by way of exfoliatin toxin.

Histopathology is the best test to confirm subcorneal acantholytic blistering diseases and conformation of PF. If Trichophyton is still a differential diagnosis then a Periodic Acid Shift PAS stain may be added to highlight fungal hyphae. When compared to the pustule formed in bacterial folliculitis the pustules associated with PF span multiple follicles. Direct immunofluorescence is not commonly performed for clinical practice cases but more used in research. Intercellular IgG is found in most feline cases and in 66-80%of canine samples. Previous steroid use may cause a false negative result and other skin diseases can result in false positive results. Indirect immunofluorescence is being worked on and was found to be unreliable as circulating IgG autoantibodies were rarely found. The substrate used caused variability in results and now it is believed there is immunological heterogeneity in canine PF.
Therapy

It is essential that a diagnosis be made prior to initiating immunosuppressive or immunomodulating drugs. There are variable responses to all the drug options used to treat pemphigus foliaceus and once immunosuppressive therapy is initiated it will be much more difficult to obtain diagnostic biopsy samples. Also it is the author's opinion that if there is only a partial response to therapy and treatment is discontinued in order to obtain diagnostic samples the disease may flare more severely and be more difficult to get under control. Pemphigus foliaceus warrants a guarded prognosis. Gomez reported a 39.5% survival over 6 years and 56% died within the first year. Of these 87% were euthanized because of drug side effects. At our practice a retrospective review of 31 cases of PF followed 1-5 years showed a 71% survival rate. Only 13% were euthanized within the first year. Half of those were due to a poor response to therapy and the other half was due to relapse after the owners discontinued the medications.

Usually the initial treatment of choice for PF is glucocorticoid therapy. In our practice about 35% of PF cases can be adequately controlled with glucocorticoid therapy alone. Glucocorticoids effectiveness relates to its effect on the humoral and cell-mediated immunity, phagocytic defenses and inhibition of inflammatory mediators. The side effects of immune suppressive doses of steroids are many and include dull scaly hair coats, muscle atrophy, polyuria, polydipsia, polyphagia, weight gain, behavioral changes, gastrointestinal changes, panting and increased risk of infections. With longer use I have seen atrophic skin, calcinosis cutis, pancreatitis, and diabetes. Failure of response to glucocorticoid therapy alone and severe side effects associated with glucocorticoid therapy that have then been referred to our clinic are some of the most rewarding cases to treat. Small Animal Dermatology states to continue the induction dose until the disease is inactive. Unfortunately this can result on patients being treated with 1-2 months of prednisone at BID dosing. Due to significant side effects these patients often will be euthanized. I typically will discuss with the owner the importance of frequent rechecks to evaluate response to therapy and side effects. I warn owners at the beginning that additional medications will be added to the treatment program if there is a poor initial response to steroids alone or if there is an inability to taper the steroids to every other day dosing. I typically will ask clients to schedule a recheck at 7-14 day intervals during the initial therapy. I will usually start with prednisone or prednisolone at 2.2 – 4.4 mg/kg. In smaller breed dogs I tend to start with 4mg/kg and with larger breeds (>80 pounds) I rarely start with more than 2.2mg/kg. I will start with this dose divided BID for 5 days and then given as a single dose daily for 5 days. Then the tapering will begin depending on the patient’s initial response. I like to see the patients back at this time. If the patient is responding well I will continue the initial daily dose of 2.2 – 4.4 mg/kg and start to taper the alternate day dose. If the patient is responding well I will taper the alternate day dose by 20-25% every 4-6 days. Not until the steroid dose is lowered to alternate day dosing will I start to taper the initial immune suppressive dose from 2.2-4.4 mg/kg.

Other glucocorticoids that may be utilized include oral triamcinolone (Vetalog, Fort Dodge) or oral dexamethasone (Azium, Schering-Plough and generics) These glucocorticoids are considered 6-10 times more potent than prednisone or prednisolone and may have fewer side effects of polyuria and polydipsia or behavioral or personality changes. Immune suppressive dosing for triamcinolone is 0.2 to 0.6mg/kg daily and for dexamethasone is 0.2 to 0.4 mg/kg daily.

Azathioprine (Imuran, Glaxo Wellcome and generics) is my first choice as an additional immunosuppressive drug in the dog. I use it as a glucocorticoid sparing agent in cases where there is still active disease after the 10 day induction with glucocorticoids. I do not use this drug in cats as it is associated with profound myelosuppression and fatal reactions. Azathioprine is an antimetabolite that interferes with nucleic acid synthesis and is cytotoxic to T cells. Its greatest effect is on T-cell dependent antibody synthesis. Again there is a dosage range with this drug of 1.5-2.5mg/kg every 24-48 hours. Adverse reactions with this drug are myelosuppression, gastrointestinal side effects and a small percentage of cases develop hepatotoxicity. This hepatotoxicity usually responds to withdraw of the medication. It is imperative that monitoring of the patients complete blood count, platelet count and liver values be monitored with this medication. The standard of care in our practice is to monitor the CBC and platelets every 2 weeks for 12 weeks. The blood counts are monitored in a table and observed for a downward trend for any of the cell types. If there is a downward trend the dose may be adjusted to a lower dosage or frequency prior to a marked drop in the blood count occurring. As discussed above with glucocorticoids I typically will use the higher dosage range in the small dogs and the lower dosage range in the larger breeds.

Chlorambucil (Leukeran, Glaxo Wellcome) is an alkylating agent that affects the cross linking of DNA. It is the glucocorticoid sparing drug of choice for cats and I have used it cautiously as an adjunctive therapy with azathioprine and glucocorticoids in refractory canine PF cases. It is dosed at 0.1-0.2mg/kg every 24-48 hours. Again monitoring of CBC and platelet counts similar to that described above for azathioprine is mandatory.

Cyclosporin (Atopica, Novartis) inhibits calcium dependent pathways especially those affecting the actions of calcineurin. This blocks regulatory proteins that up regulate activation genes of the T helper inducer and cytotoxic cells.
Initial studies of cyclosporine in treating PF had not been impressive. Those studies were prior to the microencapsulated formulas and we are seeing some cases with a good response to treatment with a dosage of 5-10mg/kg daily with 5mg/kg ketoconazole given in conjunction. The ketoconazole affects the metabolism rate of cyclosporine and it is more cost effective to use this combination therapy then raising the cyclosporine dose.

Mycophenolate mofetil (CellCept, Roche Pharmaceuticals) inhibits purine synthesis, specifically guanine thus inhibiting the proliferation of lymphocytes which are dependent on guanosine synthesis. Side effects include bone marrow suppression, nausea, vomiting, diarrhea and increased risk of infections. Doses reported 22-39 mg/kg daily divided q 8 hours. The reported success rate of therapy is 50% for canine PF.

Other options of therapy include chrysotherapy, mycophenolate mofetil, dapsone and sulfasalazine, cyclophosphamide, and IV immunoglobulin therapy. It is my impression that if you are starting to reach for these less traditional therapies it would be a good idea to refer the case to a dermatologist to get a second opinion.

### Key Drug Drug Class Dose Range Frequency Route Indications
<table>
<thead>
<tr>
<th>Key Drug</th>
<th>Drug Class</th>
<th>Dose Range</th>
<th>Frequency</th>
<th>Route</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>Glucocorticoid</td>
<td>2.2-4.4mg/kg</td>
<td>Daily then taper</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Glucocorticoid</td>
<td>0.2-0.6 mg/kg</td>
<td>Q 24-72 hours</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Glucocorticoid</td>
<td>0.2-0.4 mg/kg</td>
<td>Q 24-72 hours</td>
<td>PO</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Purine Antagonist</td>
<td>1.5-2.5mg/kg</td>
<td>EOD – daily</td>
<td>PO</td>
<td>Steroid sparing effect</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Alkylating agent</td>
<td>0.1-0.2mg/kg</td>
<td>EOD-daily</td>
<td>PO</td>
<td>Steroid sparing effect</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Immune modulating</td>
<td>5-10mg/kg</td>
<td>Daily</td>
<td>PO</td>
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</tr>
</tbody>
</table>

### Summary
Pemphigus foliaceus is an autoimmune cutaneous disease which may have a variety of underlying trigger factors, and can be a challenge to diagnose, manage and treat. The key is in getting the proper diagnosis and modifying the drug therapy based on history and clinical signs. The therapeutic plan must evaluate not only response to therapy but side effects of the medications for maximum survival rates to be obtained.

### References:
New treatment modalities for methicillin-resistant staphylococci infections in dogs
A/Prof Darren Trott BSc (Hon), BVMS (Hon) PhD,1 Elizabeth Hickey,1 Dillon Devathasan1, Dr Manouchehr Khazandi,1 Dr Meng Siak,2 Dr Mandy Burrows,2 Prof Sanjay Garg1 and Dr Stephen Page4
1School of Animal and Veterinary Sciences, The University of Adelaide; 2Animal Dermatology Clinic, Murdoch University; 3University of South Australia; 4Luoda Pharma Pty Ltd.

The need for new antimicrobials in veterinary practice
The World Health Organisation (WHO) and other national and international organisations are issuing increasingly urgent warnings that we face a double threat: a “dearth of new antibiotics in the pipeline”, and little incentive for industry to invest in R&D to overcome the looming crisis. WHO has described it as one of the greatest threats to global health.1,2

In the first half of the 20th century, a large number of antimicrobial compounds (e.g. sulfonamides in 1930s, penicillins in 1940s, and macrolides in 1950s) were discovered, which changed the landscape of human and animal health and dramatically extended life expectancy. Progress since the 1950s has been slower, with the addition of quinolones and carbapenems as major classes of antimicrobials. For a number of reasons – including the rapidity with which resistance develops to newly released compounds, increasingly demanding regulations for licensing and use, and compliance issues – the pharmaceutical industry has moved away from research on antimicrobial discovery, leading to a lack of promising therapeutic drug candidates in the development pipeline. Although a recent call3 by the Infectious Diseases Society of America for 10 new classes of drug by 2020 has reinvigorated discovery programmes around the world, any newly discovered classes will be reserved for human use only. This is a major concern as multidrug-resistant pathogens are increasingly being isolated from companion animals as causes of infection and as commensal microbiota.4

Methicillin-resistant staphylococci are increasingly recognised as both pathogens and commensals in companion animals. Methicillin-resistant staphylococcal skin infections in dogs are disseminating rapidly due to cross-transmission of successful MDR clones between individuals, with some strains showing resistance to up to six classes of drug.5 In human medicine, we are already seeing expansion of the resistance of methicillin-resistant staphylococci to mupirocin and chlorhexidine, two topically applied antibacterials most widely used to prevent colonization by hospital-acquired strains.6 As a result, it is crucial that we develop new compounds and formulations that will not be used in human medicine to manage resistant infections in dogs and other animals.

We have identified a class of antimicrobial agents (the LP series) with significant activity against methicillin-resistant staphylococci. Our preliminary in vitro work has confirmed that three compounds selected from the series are highly active against both methicillin-resistant strains of Staphylococcus aureus (MRSA) and Staphylococcus pseudintermedius (MSSP and MRSP) isolated from a range of skin infections in companion animals. Preliminary work has confirmed the viability of developing LP compounds into safe and effective veterinary delivery systems by solving formulation challenges such as poor solubility and intracellular uptake. Further pre-clinical development of the LP series as topical treatments for staphylococcal skin infections in companion animals will have significant economic, social and public health benefits as currently, members of the LP class are not used in human medicine and do not promote cross resistance to classes of drug ranked by the WHO as highly important.

Preliminary in vitro data with the LP series of compounds
The LP series of compounds we have identified in preliminary work are natural products produced by various species of the actinobacterial genera. The LP series of compounds will not be developed as parenteral therapies and have many desirable characteristics including lipophilicity for development as topical treatments for skin infections. We initially were provided with five LP compounds for preliminary screening (Table 1). However, following an assessment of fermentation yield, regulatory considerations and the results of microbiological activity screening, three compounds LP1088, LP1369 and LP6315, have been selected for further development, of which LP1369 has the most desirable physico-chemical properties and a high performance liquid chromatography (HPLC) quantification method.

In vitro antimicrobial testing of these compounds has demonstrated bacteriostatic activity against both methicillin-sensitive and methicillin-resistant staphylococci with some compounds showing bactericidal activity against selected strains at higher concentrations. A notable point is that for each individual antimicrobial compound, the MIC50 and MIC90 values did not vary significantly between the methicillin-resistant and methicillin-sensitive isolates. This indicates
that a given concentration of these five antimicrobials could be used effectively for treatment of staphylococcal infection regardless of its methicillin resistance status.

Provisional Australian patents have been filed for the activities of these compounds in skin infections. The MIC<sub>50</sub> and MIC<sub>90</sub> values and narrow ranges for all isolates indicate that achievable concentrations applied topically would be effective against key infections caused by these organisms. The <em>in vitro</em> antimicrobial activities we have observed and the history of use of these compounds in lower-order animals strongly suggests that they are promising candidates for use in veterinary applications, including our major target: skin infections and bovine mastitis.

Table 1. Comparative MICs (µg/ml) for five novel LP antimicrobials and ampicillin for methicillin-sensitive (MSSP) and methicillin-resistant (MRSP) isolates of Staphylococcus pseudintermedius and methicillin-resistant Staphylococcus aureus (MRSA) isolated from companion animals in Australia. Each MIC test was performed in duplicate.

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>ampicillin</th>
<th>LP1088</th>
<th>LP1369</th>
<th>LP4525</th>
<th>LP6315</th>
<th>LP9666</th>
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<tbody>
<tr>
<td>MSSP (n=24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
<td>8</td>
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<tr>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>128</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>4</td>
<td>32</td>
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<tr>
<td>MIC range</td>
<td>0.25 - &gt;128</td>
<td>0.5 - 2</td>
<td>0.5 - 2</td>
<td>0.25 - 0.5</td>
<td>1 - 8</td>
<td>2 - &gt;128</td>
</tr>
<tr>
<td>MRSP (n=17)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>64</td>
<td>1</td>
<td>1</td>
<td>0.25</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>&gt;128</td>
<td>8</td>
<td>4</td>
<td>0.5</td>
<td>4</td>
<td>&gt;128</td>
</tr>
<tr>
<td>MIC range</td>
<td>0.25 - &gt;128</td>
<td>0.5 - 16</td>
<td>0.25 - 4</td>
<td>0.25 - 0.5</td>
<td>1 - 4</td>
<td>1 - &gt;128</td>
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<tr>
<td>MRSA (n=6)</td>
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<td></td>
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<tr>
<td>MIC range</td>
<td>16 - &gt;128</td>
<td>0.5 - 1</td>
<td>0.5 - 2</td>
<td>0.25 - 0.5</td>
<td>2 - 8</td>
<td>8 - &gt;128</td>
</tr>
</tbody>
</table>

Topical safety studies in mice

A large amount of safety data has already been collected on the LP compounds. Nevertheless, our most promising LP topical formulations will be tested for safety in mice using a full thickness skin defect model. Full thickness 6 mm diameter skin defects will be made on the shaved and aseptically prepared backs of 6-8 week old male anaesthetised C57BL/6 mice using a biopsy punch (six mice per treatment group). Concentrations of the LP formulation in 100 µl volumes (1-2% w/v) will be directly applied to the wounds twice daily for two weeks. The cutaneous wounds will be assessed and the mice observed twice daily for clinical signs and/or changes in demeanour including any pain response on topical application. At the conclusion of the observation period, mice will be euthanized and submitted to full post-mortem examination including skin histopathology to confirm the safety of the topically administered LP formulation. Following on from these experiments, a partial thickness burned skin mouse model will also be investigated.

Topical efficacy studies in mice

We have ethics approval to develop a cutaneous wound infection model using bioluminescent <em>S. aureus</em> strains in C57BL/6 mice. As outlined above, a full thickness 6 mm diameter skin defect will be made on the shaved and aseptically prepared backs of 6-8 week old anaesthetized male mice using a biopsy punch (five groups of six mice each per experiment). The wounds will then be inoculated with 1 x10<sup>7</sup> CFUs of bioluminescent <em>S. aureus</em> to establish a cutaneous infection. Treatments will begin 4 hours after initiation of the infection and will continue twice daily for up to 7 days. For non-invasive bioluminescent imaging of the infection using the Xenogen IVIS imaging system, mice will be anaesthetized with isoflurane and imaged daily for 10-14 days. Treatment groups will include no treatment and sham inoculated (formulation only) control, the LP treatment (1-2% LP1369 in hydrogel or ointment formulations) and a group treated with 1% mupiricin ointment as a positive control. The most recent results from these animal trials will be presented.
References
What is meant by ‘methicillin resistance’ when describing Staphylococcus species?

In many respects the term ‘methicillin resistance’ is misleading. While it suggests resistance to a single penicillin antibiotic (methicillin), it actually refers to an almost ‘pan-beta-lactam resistance’ resulting from a structural change in penicillin binding proteins in the bacterial cell wall. As such the term ‘methicillin resistance’ falls short of describing the major significance to human and veterinary medicine.

The bacterial cell wall in both gram positive and negative bacteria have an important layer known as peptidoglycan, which creates the shape of the bacterial cell and more importantly strengthens the cell wall, preventing it from bursting from the enormous osmotic gradient created by the bacteria’s high intracellular solute concentration. Peptidoglycan has many layers especially in bacteria such as Staphylococcus, which are bound together by chains of amino acids (see Figure 1a-1d) that are crosslinked thanks to the important enzymes transpeptidase and N-acetyl carboxypeptidase (aka penicillin binding proteins) in the cell wall of the bacterium. Therefore ‘methicillin resistance’ refers to alterations in the structure of the penicillin binding proteins, resulting in a failure of beta-lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams and penems) to bind and have their usual effect on weakening cell wall synthesis.

Figure 1: Beta-lactams – mechanisms of action and resistance [YouTube Video](http://www.youtube.com/watch?v=qBdYnRhdWcQ)
Some staphylococci produce an enzyme that destroys the beta-lactam ring (beta-lactamases) and methicillin was first developed in the 1960s as a beta-lactamase resistant antibiotic. While methicillin had a short period of usefulness it was quickly ceased as a therapeautic agent due to side effects and is no longer used for in vitro testing. However, the beta-lactam resistant *Staphylococcus* strains which developed with a year or so of the introduction of methicillin were named ‘methicillin resistant’ and the name has lingered 50+ years later. While some methicillin resistant *Staphylococcus* species have resistance to other categories of antimicrobial agents, determining whether an isolate is also multi-drug resistant (MDR; non-susceptible to at least one agent in 3 or more categories of antimicrobial agents) or extensively drug resistant (XDR; non-susceptibility to at least one agent in all but two or fewer antimicrobial categories i.e. bacterial isolates remain susceptible to only one or two categories) requires thorough antimicrobial susceptibility testing be performed.1

How do we know if an isolated *Staphylococcus* species is ‘methicillin resistant’?

‘Methicillin resistance’ is commonly mediated by the mecA gene which codes for the supplemental penicillin binding protein 2A (altered transpeptidase) and is expressed homogeneously (all bacteria) or heterogeneously (more difficult to detect phenotypically as only a fraction of the bacterial population express it so care is needed in antimicrobial susceptibility testing). Laboratories performing antimicrobial susceptibility testing must abide by the Clinical and Laboratory Standards Institute (CLSI) standards, an internationally agreed set of standards established for each genera or in some cases species of bacteria as in the case with some *Staphylococcus*.

Oxacillin is the preferred penicillinase-stable penicillin used for *in vitro* testing and the results are applied to other penicillins, meaning that non-susceptibility to oxacillin infers the same for all beta-lactam antimicrobial agents. Substituting oxacillin, a narrow spectrum penicillin, for another penicillin has been desired by laboratories and extensive benchmarking has led to the acceptance by CLSI standards of cefoxitin to predict mecA mediated resistance in *Staphylococcus aureus* and coagulase negative *Staphylococcus sp*. In fact for those species listed cefoxitin is more specific. However caution needs to be applied when extrapolating methods across to *Staphylococcus pseudintermedius* as the breakpoint (≤21 mm=oxacillin resistant, and ≥22 mm=oxacillin susceptible) used in *S.aureus* cannot be applied to *S.pseudintermedius*. This has been well illustrated in a recent article by Meng Siak and Mandy Burrows2 using *S.pseudintermedius* isolates from dogs with pyoderma (MRSP and MSSP) which cross checked the accuracy of ‘methicillin resistance’ using mecA polymerase chain reaction (PCR), phenotypic resistance to oxacillin and cefoxitin. This study illustrated that to avoid underreporting of MRSP, higher breakpoints (≤30 mm=oxacillin resistant and ≥31 mm=oxacillin susceptible) are more suitable in identification of methicillin resistant *S. pseudintermedius*. It also reminds veterinary laboratories to follow CLSI standards and to ensure extrapolations from human isolates are verified to be useful and relevant in veterinary isolates.

Are MRSP home grown or imported? The Australian story so far

The origin of mecA in general is uncertain but some have suggested it originated within *Staphylococcus sciuri*, a coagulase-negative bacterium of animal origin. Irrespective, the transmissible mobile DNA element called SCCmec which contains the mec gene complex (including mecA gene, genes that control expression of mecA etc), can be transferred from one *Staphylococcus* to another of the same or different species. This level of transmissibility from other *Staphylococcus* species, makes it more likely that MRSP is home grown. While Australia is yet to experience the level of impact MRSP has had on small animal practices in the USA and Europe especially specialties such as dermatology and surgery, we have proof through archived *Staphylococcus* isolates at Faculty of Veterinary Science, University of Sydney that MRSP has been here in Australia for over 30 years.

In the last 12-18 months, considerable work has been conducted in Australia on veterinary methicillin resistant *Staphylococcus* (MRSP) in small animal practice, including MRSP and the results of these are soon to be published. Meng Siak and Mandy Burrows (Murdoch University) and colleagues have described and characterized several MRSP in dogs with bacterial pyoderma, mostly with underlying atopic dermatitis.2,3 Linda Vogelnest and I (University of Sydney) have helped to lead clinically based surveillance projects on the prevalence of MRSP in dogs with superficial pyoderma with resident Phillipa Ravens4 and honours student Eloise Ewen,5 the later study finding ~20% MRSP and 3% MRSA in dogs presented to referral dermatology practice. An analysis of clinically relevant *Staphylococcus* species isolated from a range of clinical infections in cats and dogs presented to the University of Sydney Teaching Hospital, Sydney which were submitted to our Veterinary Pathology Diagnostic Laboratory between October 2010 and Jan 2013, has found 25% of canine-derived and none of the feline-derived samples yielded isolates that were MRSP.6 The canine MRSP isolates mainly consisted of MRSP. Darren Trott and Sam Abraham have led a 9 month Australia wide surveillance study (Jan-Sept 2013) of coagulase positive *Staphylococcus* causing clinical infection in animals, isolated by Australian Veterinary Diagnostic labs (n=22). MRSP as determined by phenotypic resistance to oxacillin was found
in 10% of isolates. The 1500+ *Staphylococcus* isolates in this study, kindly funded by Zoetis, will form the basis of work to be conducted with the kind support of ARC linkage funding (LP130100736: “Superbugs and veterinary drugs: Are multidrug-resistant zoonotic pathogens residing in Australian animals?” Trott, Schembri, Norris, Gibson, Beatson), in which further characterization of these *Staphylococcus* isolates will be performed. Future studies will look beyond antimicrobial resistance to analyse the virulence factors that may be present in clinically relevant isolates in Australia as well as typing to determine their relationship to overseas cousins and archived national isolates. Home grown sleepers? or international terrorists? – Watch this space!! We are beginning an intensive period of research in this area over the next 12-18 months which may help to answer this question.

References
Managing microbial infections is often the key to successful management and long-term control of primary diseases in veterinary dermatology cases. Since cases of bacterial pyoderma are often associated with substantial levels of pruritus in the dog, control of the infection is often critical to the management of the associated pruritus. As the most common underlying cause of recurrent infections is allergic skin disease, this can often create a confusing situation for the practitioner and client. Chronically pruritic dogs assumed to be refractory allergic patients in many cases have chronic unresolved bacterial infections. Cases become more challenging when infections associated with resistant bacterial organisms are encountered. Several types of resistance among different bacterial organisms have been reported, however methicillin-resistant staphylococci (MRS) have become the most significant for veterinary patients. MRS have become increasingly problematic in humans and animals worldwide. Some geographic variation exists and Australia/New Zealand appears to be a region in which resistant bacterial organisms are not as prevalent as in other parts of the world. Although knowledge on the global infection epidemiology of methicillin-resistant *S. pseudintermedius* (MRSP) is still scarce, spread of a limited number of MRSP clones is believed to occur. Currently it is believed that the genetic background of MRSP is associated with its geographic origin, i.e. certain dominating MRSP-lineages spread in Europe or the North American continent. Two clonal populations of MRSP represented by ST68 in North America and ST71 in Europe were originally described as predominant strains within their regions. Recent studies, however, have identified additional strains, some of which are genetically closely related, others that appear to represent additional clonal complexes and others that may have more recently acquired methicillin resistance. Recent data suggest that MRSP clonal populations continuously arise and spread, however, they remain primarily concentrated within distinct geographical regions.1

In areas where MRS has become increasingly prevalent, the veterinary practitioner has had to respond with modified strategies for both topical and systemic therapy. It has become essential to initiate both appropriate topical and systemic therapy. Topical therapy is often used as an adjunct to systemic antibiotics because it speeds the healing process, aids in elimination of bacterial by-products and generally makes the patient feel better. Topical therapy can also be used as a preventative strategy particularly in cases prone to recurrent infection. Systemic antibiotic therapy is indicated in most cases of pyoderma and selection of the antimicrobial agent often reflects the underlying primary disease, predisposing factors, and the degree and severity of scarring or chronicity of infection. Culture and sensitivity testing is usually indicated for appropriate antibiotic selection, especially when dealing with MRS infections. By understanding the current status of bacterial resistance and being aware of the recommendations for topical and systemic therapy, dermatologists and veterinarians working in general practice in Australian and New Zealand can be well prepared to handle these infections as they become more common in dermatology patients.

**Background**

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been recognized in humans for more than 40 years but has become a significant pathogen over the past 10 to 15 years and is now considered a potentially serious concern because of its limited antibiotic sensitivity. In humans, most cases of MRSA are associated with hospitalisation (MRSA-HA) because they are seen in patients who have been hospitalised or who have had invasive procedures. Community-associated MRSA (CA-MRSA) occurs in humans who have no history of risk factors for MRSA. Isolates of this type of infection tend to differ genetically from hospital-associated MRSA. Many express a toxin called Panton-Valentine Leukocidin and can create skin and soft tissue infections, life-threatening necrotizing fasciitis (i.e., “flesh-eating bacteria”), necrotizing pneumonia, and sepsis in some cases. Common sources for community-associated MRSA are gymnasiums, locker rooms, and other warm, humid locations in which close contact between humans occurs.

Veterinary patients can acquire MRSA from the environment, humans or other infected animals. Most veterinary cases of MRSA colonisation do not develop clinical disease but may be more at risk for MRSA after surgical or other invasive procedures. Most importantly, they can serve as a source for recolonizing humans within their environment.
The more common MRS species in cases of canine pyoderma, including *S. pseudintermedius*, *S. intermedius*, *S. schleiferi*, and *S. hyicus*, have emerged as a growing concern in veterinary medicine. However, unlike MRSA, these veterinary strains are not considered to be zoonotic in most cases, but they can be transmitted from patient to patient in a hospital environment, creating a significant endemic problem in some veterinary hospitals.

In all MRS infections, strains may appear sensitive to some beta-lactam antibiotics in vitro, including cephalosporins, but they exhibit cross-resistance in vivo. MRS may also be resistant to multiple non-beta-lactam drugs, like aminoglycosides, macrolides, tetracyclines, chloramphenicol, and fluoroquinolones. MRS infections should be suspected when oxacillin-resistant or multidrug-resistant staphylococci are isolated from clinical infections. Oxacillin is used instead of methicillin because it is more stable and better standardized for disk diffusion susceptibility testing.

Understanding how bacterial resistance develops requires basic knowledge of the beta-lactam ring, which is part of the structure of several antibiotic families: penicillins, cephalosporins, carbapenems, and monobactams, which are therefore also called beta-lactam antibiotics. These antibiotics inhibit bacterial cell wall synthesis. Because use of beta-lactam antibiotics is common, certain bacteria have been able to develop alternative methods of resistance. An enzyme called beta-lactamase is present in many different types of bacteria, and this enzyme “breaks” the beta-lactam ring, destroying the antibiotic’s effectiveness. As a response to bacterial resistance to beta-lactam drugs, additional antibiotics have been developed that counteract or block beta-lactamase. However, as a response to the decreased efficacy of beta-lactamase, some bacteria have changed the proteins in their cell walls, called penicillin-binding proteins (PBPs), to which beta-lactam antibiotics bind. Because the PBPs are no longer recognized by the beta-lactams, the antibiotics are ineffective. This is the mechanism behind the development of MRS infections. The methicillin resistance results from the mecA gene that encodes for the production of the altered penicillin-binding protein 2a (PBP2a). This protein has a low affinity for, and gives complete resistance to, all beta-lactam antibiotics. A method of testing to help identify new emerging strains of MRS is to detect this mecA gene by way of polymerase chain reaction assay.

It is important that pet owners be informed when their dog has MRS infection, especially if the isolate is identified as MRSA in repeated bacterial cultures or if the owner is immunosuppressed or has a severe illness. Zoonotic infections are a concern with MRSA but are less likely with the more commonly isolated MRS seen in veterinary medicine. It has been shown that veterinarians and staff have a higher prevalence of subclinical nasal carriage of MRSA strains than the general US population, and that people living in close physical contact may be colonized by identical strains of MRSA. One hundred and seventy-one veterinary dermatology practice staff and their respective pets (258 dogs and 160 cats) were screened for MRSA, *MRSA pseudintermedius* (MRSP) and *MRS schleiferi* (MRSS). Genetically identical strains, as determined by pulsed-field gel electrophoresis, were isolated from five people and their respective pets: MRSA in two people/three pets and MRSP in three people/four pets. There were no demographic or epidemiologic factors statistically associated with either human or animal carriage of MRS, or with concordant carriage by person–pet pairs. However, the MRSA isolation rate for people in this study (3.5%) exceeded that documented for the general US population (0.84%) by a factor of 4. A study from Australia also looked at the nasal carriage rates of MRSA from veterinarians. Samples obtained from veterinarians attending conferences showed that among the 771 respondents ‘industry and government veterinarians’ (controls) had the lowest prevalence of MRSA carriage at 0.9%. Veterinarians with horses as a major area of work emphasis had a prevalence of 11.8% (13-fold that of controls) and those whose only major emphasis was horses had a prevalence of 21.4% (23-fold that of controls), although the rates of MRSA isolates from horses in Australia have been reported to be low. Veterinarians with dogs and cats as a major activity had a 4.9% prevalence (5-fold that of controls). Prevalence rates for other major activities (pigs, dairy and beef cattle, avian and wildlife) were also increased, but were estimated from smaller numbers of respondents.

The prevalence rates of MRS in dogs ranges from 0.58 to 30%, but comparison of studies is difficult due to differences in the populations sampled; healthy vs diseased, hospitalised vs outpatients and sites of sample collections. Risk factors for the development of MRS in dogs appear to be related to the use of previously used antibiotics, previous hospitalization, living in an urban environment and older age of the affected animal. A recent study looked at the prevalence of methicillin resistance between a primary care hospital and a veterinary referral university hospital and there was no difference between the isolates of MRS, however previous antimicrobial therapy was an important risk factor for the isolation of MRS at both sites.

Another recent study in Germany evaluated the association of MRS carriage and a number of epidemiological factors in an attempt to characterise risk factors. In the final model, cats (compared to dogs), animals that had been hospitalised, or visited veterinary clinics more frequently and those that had received topical ear medication or glucocorticoids were at higher risk of MRSP infection, whereas *S. pseudintermedius* isolates from ears were more
likely to belong to the MSSP group. These results indicate an association of MRSP infection with veterinary clinic/hospital settings and possibly with chronic skin disease. There was a lack of association between MRSP and antimicrobial therapy that has been implicated previously in some studies.\(^9\)

The frequency of MRS organisms detected does appear to vary geographically. In another recent study that assessed the susceptibility patterns of *Staphylococcus (pseud)intermedius* organisms isolated from cases of superficial pyoderma in South Africa from 2007-2010, only 3 of 319 organisms were cultured as methicillin-resistant. These samples were submitted to a diagnostic laboratory from across South Africa. Although this was not the aim of this study, no speculation was offered for the low numbers documented from this study geographically.\(^10\) Compare this to the earlier study from staphylococcal isolates submitted to the diagnostic lab at a veterinary school in northern California in which 89 staphylococcal isolates from the VMTH showed that 34 (38.2\%) were methicillin resistant. And of 33 primary clinic isolates, nine (27.3\%) were methicillin resistant. Multiple drug resistance was identified in 41 of 53 (77.3\%) MRS isolates from the VMTH and five of nine from the PCC.\(^8\) These showed no differences in risk between referral specialty clinic and primary care factors. Risk factors identified for both groups were antibiotic treatment within the last year and for VMTH and hospitalization of dogs within the last year. However the sheer numbers of positive results were substantially higher than in the results from the South African study. The previously referenced German study reported 2130 *S. pseudintermedius* isolates of which MRSP accounted for 11.6\% (248/2130).\(^9\)

The percentages from Germany are similar to the results reported from a Japanese study in which two hundred S. *pseudintermedius* isolates (22 isolated from cats and 178 from dogs) were collected from animals with dermatitis across south Japan (Kyushu area) between 2008 and 2010. Of the 200 S. *pseudintermedius* isolates collected, 27 (13.5\%) were characterized as MRSP. ST71 was the most common group lineage characterized in this study although a new emerging lineage known as ST26 were also noted.\(^11\)

A linear increase based on year has also been found in a study from the southern US in which the prevalence of MRS isolated from culture results increased from 6\% of *Staphylococcus* isolates (45/722) in 2002, 11\% (98/857) in 2005, 19\% (181/977) in 2008 and 32\% (256/794) in 2011.\(^12\)

In a preliminary study reported from Australia, 10\% of 193 isolates were found to be MRSP by demonstrating resistance to oxacillin on susceptibility.\(^13\)

**Co-Infection with multiple Strains**

Another emerging issue has been the finding of co-existent infections of more than one strain of *Staphylococcus* organism isolated from one location or on one patient. There are few reports of this phenomenon but the author has documented this in multiple cases clinically and some of this information will be reported as well. In some cases these may be two strains in which one is MRSP and the other MSSP while in others two differing strains of MRSP are isolated demonstrated by various resistance profiles. One recent study reported results from a dog with otitis externa in which two different *S. pseudintermedius* strains were isolated. The staphylococcal isolates occurred in a mixed flora also containing *Pseudomonas aeruginosa* and *Malassezia pachydermatis*. The staphylococcal isolates were subjected to species determination and were further tested for antimicrobial resistance and mecA content. These investigations confirmed presence of two *S. pseudintermedius*, one with mecA and the other without. The strains had different resistance profiles and belonged to different STs; The MRSP to ST129 and the MSSP to ST120. In both cases there was no clear difference in colony morphology on blood agar.\(^14\)

The clinical relevance of this is that it may complicate the ability of the clinician to adequately manage cases. The presence of multiple strains of the same organism may be missed by laboratories when assessing agar plate morphology and characteristics. Multiple such cases have been noted and it is the author’s impression that these cases do require more aggressive management both orally and topically.

**Culture and Sensitivity**

Culture and sensitivity testing is indicated in cases that have not responded to appropriate empirical therapy based on cytology, in cases of suspected MRS infections, in cases of severe immune suppression, and when there is a differential diagnoses that includes a sterile inflammatory disease. Depending on the type of lesion and the differential disease, the culture may be obtained by using a sterile swab or preferably by using a sterile biopsy punch technique. The sample is then sent to the lab; the tissue is emulsified and then cultured. Lesions that are not already open to the surface are the best samples to obtain. Deeper, and in particular more nodular or granulomatous lesions, may require additional culture techniques in the laboratory. Culture and sensitivity testing has been particularly valuable in identifying the increasing frequency of MRS infections. Assume methicillin resistance if an organism is reported as
being oxacillin-resistant. If oxacillin is resistant, the lab should ideally report all beta-lactam agents as resistant even if in vitro testing shows susceptibility.

Work in human and now veterinary medicine has looked at resistance prevention by using a newer concept called “the mutant prevention concentration” (MPC). MPC can help evaluate an antibiotic’s ability to minimize or limit development of resistant organisms. The MPC defines the antimicrobial drug concentration threshold that obtains inhibition of fully susceptible, as well as resistant, strains of bacteria. Another definition is the drug concentration that prevents growth of first-step resistant mutants or the MIC of the most resistant organism present in the heterogeneous bacterial population when tested against ≥10⁹ organisms. A mutant section window (MSW) describes a danger zone in the dosing of antibiotics at which drug concentrations in serum or other body fluids is considered too low and resistance is likely to occur. Ideally antibiotics should exceed the MPC and be in the upper end of the mutant section window. MPC testing has been established for many fluoroquinolones but is now available for many other antibiotics. Much of the data show the importance of using antibiotics at or above their recommended dosing during the early stages of therapy, during treatment of the infection, and beyond clinical resolution.¹⁵,¹⁶

**Antibacterial Therapy**

Therapy for successful eradication and control for MRSP infections in animals as with MRS infections in humans has been shown to be variable and multifactorial. Both topical and systemic therapy can be utilised and in our experience while systemic therapy is beneficial in most cases of MRSP infections in dogs the addition of aggressive topical therapy we believe provides a more rapid response. In addition, since many of the cases that we see as dermatologists are patients with concurrent skin disease such as atopic dermatitis which may have cutaneous barrier defects allowing for impaired barrier function and/or require immunomodulating therapy it is our clinical impression that without appropriate long term topical management therapy relapses are more common. The following sections contain information regarding topical and systemic therapies that are utilised in our practices.

**Topical Therapy**

Topical therapy should be used in all cases of pyoderma. It can be of particular value in treating and controlling chronic recurrent cases. It usually decreases bacteria and reduces surface recolonisation, helping to prevent recurrences. There are many topical antimicrobial vehicles: shampoos, whirlpools, soaks, rinses, sprays, lotions, gels, creams, and ointments. Shampoos are the more practical and effective. Whirlpools and soaks are more labour-intensive and require additional equipment. For localized lesions, sprays, lotions, gels, creams, and ointments can be used. The author prefers not to use heavy occlusive vehicles for moist, exudative lesions, as they tend to slow healing and drying and may spread infection.

**Shampoos**

Shampoo therapy is the author’s favourite topical antimicrobial therapy. It removes inflammatory by-products and can give immediate results. This is particularly important for some owners and pets. The owner does not need special equipment, and it can be done at home. The frequency depends on the severity of the case and the owner’s willingness to do the work. Cases of pyoderma benefit from frequent bathing (every 2 to 3 days) initially, followed by weekly maintenance.

The most common antibacterial agent found in shampoos in Australia is chlorhexidine. It is generally well tolerated and is not drying or irritating and at 2-3% concentrations in shampoo formulations have generally been found to be clinically effective. However, newer formulations with 3% or higher have been quite impressive in clinical cases and are available commercially. Recently multiple in vivo and in vitro studies have demonstrated the efficacy of chlorhexidine and chlorhexidine containing shampoo formulations on both methicillin sensitive and methicillin resistant *S. pseudintermedius* strains.

One study with *S. pseudintermedius* organisms collected from dogs with superficial pyoderma reported the minimum inhibitory concentration (MIC) to be 1 microgram/kg for both chlorhexidine gluconate and acetate.¹⁷ While another study reported chlorhexidine digluconate to have an MIC of 4-8 micrograms for both methicillin sensitive and resistant strains of *S. pseudintermedius*. A simulated in vivo study looked at the residual effects of chlorhexidine on the hair shafts of dogs bathed with various concentrations; 0.8%, 2%, 3% and 4% chlorhexidine containing shampoos. Dogs were bathed and hairs were removed immediately and then again at 2, 4 and 7 days after bathing. These hairs were inoculated onto a culture agar plate streaked with *S. pseudintermedius* organisms. Zones of inhibition around the hair shafts were then measured to assess antimicrobial activity that was present around the hair. There was inhibition noted even at 7 days in some cases. Efficacy was noted to be greater in 2% and 3% containing shampoos however other factors including shampoo formulation are likely to have played a role in the final results.¹⁰ In addition, factors
such as the ability to penetrate into the hair follicle and deeper layers of the epidermis may affect the efficacy of various formulations of chlorhexidine-containing shampoos. However given the increasing prevalence of more resistant strains of *Staphylococcus* noted in clinical dermatology, these studies suggest that the role of topical therapy is a critically important factor in managing bacterial infections in the canine.

Two other antimicrobial agents are triclosan and ethyl lactate. These products are considered non-irritating but the author does not routinely use them because of the superior effectiveness of chlorhexidine. However, they can provide adjunctive therapy in management of keratinization defects with concurrent pyoderma.

**Localized Treatment Options (Chlorhexidine sprays and bleach)**

Localized topical therapy has specific indications. It is used most commonly for pyotraumatic dermatitis, skin-fold pyoderma, and localized folliculitis and furunculosis. Several companies that make chlorhexidine-based shampoos also make topical sprays, wipes, and towelettes that can be used between or as an option for bathing. Some clients that have difficulty with performing routine shampoo therapy because of the size or the nature of the patients sometimes find benefit with these topical approaches which can be applied with generally less stress for both client and patient. Daily use of chlorhexidine containing products in the form of sprays or wipes may be helpful in treating active infections by increasing the time exposure of the antimicrobial activity on the skin. Once the infection has been resolved, the author often uses the spray formulations twice weekly with patients that have shown to be predisposed to relapsing infections regardless whether those strains are MRSP or MSSP.

Sodium hypochlorite (bleach) has been a disinfectant that is commonly used in human and veterinary hospitals. There are general recommendations regarding the use of bleach bathing for decontamination of humans with MRS infections used at 2.5 microliters/ml (which equates to approximately one-quarter to a half cup of bleach per bath tub). This is used as a soak twice weekly and has generally resulted in good efficacy with control of colonization in association with other therapies. Generalized xerosis of the skin is the only commonly seen side effect. Recently bleach has become more commonly used in veterinary practices as well and there are numerous recipes that have been touted although none have undergone rigorous double-blinded studies. A recent study did test 12 isolates of MRSP strains obtained from a clinical laboratory with various concentrations of bleach (6.15%). The results showed that all strains had a minimum bactericidal concentration of 1:32 but most isolates showed MIB between 1:64 and 1:128. Topical bleach sprays and rinses have become increasingly utilised in our practices with generally good response. These are often used 2-3 times weekly as adjunctive therapy. Xerosis of the skin is also not uncommonly seen in veterinary patients. Change of coat colour has been noted as well. Further studies looking at effective concentrations and frequencies are indicated since bleach can be an inexpensive and effective therapy.

**Mupirocin**

Mupirocin is available in a polyethylene glycol ointment base. It functions by inhibiting bacterial protein synthesis and has excellent tissue penetration. It should not be used on mucosal surfaces or in areas where large amounts of polyethylene glycol can be absorbed due to potential for nephrotoxicity. Mupirocin is an antibiotic derived from fermentation of *Pseudomonas fluorescens* that specifically and reversibly binds to iso-leucyl transfer RNA synthetase in bacteria. This binding causes interrupted bacterial protein synthesis and inhibited bacterial RNA synthesis.

Because of the intracellular mechanism of action, mupirocin can be used topically for treatment of multidrug-resistant *Staphylococcus* spp., even methicillin-resistant strains. Mupirocin dosage has been 2 to 3 times daily for humans, and the authors typically use this same regimen for dogs. The ointment is found as a 1% in petrolatum or generic in a polyethylene glycol vehicle. It has been used extensively for intranasal decolonization of *S. aureus* in humans. The author finds mupirocin to be particularly effective in localized lesions or in spot treating individual lesions that are not responding completely to appropriate topical and systemic therapy. Because of the concern for developing resistance widespread use of mupirocin should be avoided and there is growing sentiment that it should be reserved for clinically proven MRS strains of Staphylococcus. A recent study from the US reported that only 1 of 581 isolates of methicillin resistant *S. pseudintermedius* showed resistance to mupirocin and carried the high-level mupirocin resistance gene, ileS2 on a plasmid.

**Nisin**

Nisin is an antimicrobial peptide produced by *Lactococcus lactis*. Nisin is marketed in the US as a dairy teat wipe (Wipe Out [ImmuCell Corporation]) for prevention of bovine mastitis, and in particular for its ability to control common bacterial pathogens including some methicillin-resistant *Staphylococcus* spp. A recent study looked at nisin as sole therapy and as combined therapy with systemic antibiotics in canine pyoderma. In the nisin-only treatment group there was some benefit in dogs with *S. pseudintermedius*. In the group treated with nisin and antibiotics, the topically treated group with
nisin had their *S. pseudintermedius* lesions clear more rapidly than a non-nisin antibiotic-treated group. The study suggested efficacy in treating some dogs with bacterial pyoderma and warrants further evaluation. These products have been used in the author’s practice for some time. They are particularly effective in short-coated breeds or in areas where lesions are readily accessible with the wipe.

**Systemic Therapy**

When selecting antibiotic therapy for pyoderma including MRS infections, one should keep in mind the basic principles of successful systemic antibiotic therapy. These include proper choice of antibiotic and establishment of the effective dose and correct duration of therapy. This becomes all the more critical when dealing with resistant strains of bacteria. When MRS is suspected; antibiotic selection should be based on culture and sensitivity. Multidrug resistant infections associated with MRS isolates will dictate the most appropriate drug choice and antibiotics including beta lactams and cephalosporins commonly used for MSSP infections will be ineffective. Culture and sensitivity results are based on the MIC for serum, not tissue. Tissue MICs are different and may help to explain why antibiotics may not be effective in vivo. The MPC, discussed in the culture and sensitivity section, is better than using MICs. The MPC defines the antimicrobial drug concentration threshold that obtains inhibition of fully susceptible as well as resistant strains of bacteria. In the future, knowing the MPC for many of the commonly used antibiotics should help when determining antibiotic dosages for specific types of bacterial infection. Optimally, antibiotics should exceed the MPC, thereby eliminating infections more rapidly and reducing the risk for resistance. Much of the data show the importance of using antibiotics at or above their recommended dosing during the early part of therapy, and adequate duration of therapy beyond clinical resolution is critical. Some antibiotics can concentrate in more inflamed tissue. This is true of the fluoroquinolones, where skin concentrations are generally higher in more chronic cases of deep pyoderma vs. superficial pyoderma.

It is very important to follow the minimum recommended dose regimen to achieve optimum results. There is also a wide range of dose regimens, depending on the severity, chronicity, and scarring of the pyoderma. The author has achieved excellent results using higher-than-recommended doses of antibiotics and even combined antibiotics (i.e., cephalaxin and fluoroquinolones) in cases of deep pyoderma with severe scarring. Side effects of higher doses and combined regimens occur occasionally but are rare. Gastrointestinal upset is the most common side effect seen. However, practitioners should review the potential side effects from pharmacology references when using very high dose protocols or when combining antibiotics. Antibiotic therapy needs to be continued until the pyoderma resolves and then for 2 weeks beyond clinical cure for superficial pyodermas and 3 to 4 weeks beyond for deep pyodermas. This usually requires 3 to 6 weeks for superficial and 6 to 12 weeks or longer for deep pyodermas. Mortality rates are not significantly different between MRSP and MSSP infections; the lack of a significant difference suggests that MRSP is inherently no more virulent than MSSP, provided the infection is properly diagnosed and appropriate treatment is initiated.

The following discussion is a brief overview of the most commonly used antibiotics for MRS infections at ADC veterinary dermatology referral practices in Southern California. We evaluated the last 200 culture and susceptibility results that isolated *Staphylococcus* organisms from the skin and reported the topical and systemic antibiotic selection selected for these patients.

The most commonly used antibiotics based on the typical culture/sensitivity results for MRS infections at our practices in the US include clindamycin, trimethoprim-potentiated sulfonamides, fluoroquinolones (ciprofloxacin and marbofloxacin), doxycycline/minocycline, chloramphenicol, rifampicin and amikacin.

Clindamycin is a lincosamide, which differs from lincomycin only by the presence of a chloro substitution, which increases antimicrobial activity. Unlike penicillin and cephalosporin, it does not have a beta-lactamase enzyme. Therefore, bacteria that produce these enzymes are often susceptible to clindamycin, making it an option for some MRS pyodermas. It is bacteriostatic, and resistance problems can occur. It has high oral bioavailability and a large volume of distribution and therefore penetrates tissues well. The author likes this antibiotic for deep scarring pyodermas but uses it at a higher dose 10 mg/kg q 12 h. One study showed efficacy at 15 to 20 mg/kg q 24 h, making it more client-friendly. Side effects are minimal but can include gastrointestinal adverse events.

The trimethoprim-potentiated sulfonamides have good efficacy for canine pyoderma. Major advantages are reduced expense with generics and twice-a-day dosing. The major disadvantages are its association with drug reactions, keratoconjunctivitis sicca, and thyroid gland hypoplasia. Cutaneous and non-cutaneous drug reactions can occur. Cutaneous reactions include macular–papular eruptions, erythema multiforme, toxic epidermal necrolysis, and...
Another antibiotic used for its ability to penetrate scarred, walled-off areas of infection but also very effective against rifampicin, 5–10 mg/kg q 24 h) is a bactericidal antibiotic that not only has excellent tissue penetration but is also capable of killing Staphylococcus species intracellularly. The other disadvantage of rifampicin is the potential for hepatotoxicity, and it is contraindicated in dogs with pre-existing liver disease. Rifampicin will often produce orange-coloured urine due to a metabolite so clients should be cautioned that this may occur. To monitor for potential toxicity, complete blood counts, liver screens, and urinalysis should be performed done 2 to 3
weeks. Rifampicin is generally used for 4 to 8 weeks and we have found that as the cases of MRSP have become increasingly more common, we are choosing this drug choice more and more commonly as well due to multi-drug resistant MRSP culture results.

Amikacin is an option that is utilised occasionally in the author’s practice and in cases of multi-drug resistant Staphylococcus infections although it must be administered parenterally. When used for treatment of pyoderma, it may be administered subcutaneously by the client at home which can be a benefit as opposed to having to be hospitalized. The primary adverse effect of concern is nephrotoxicity, specifically renal proximal tubular necrosis. Amikacin may be less nephrotoxic than other aminoglycosides, particularly gentamicin. Urinalyses should be frequently monitored for signs of nephrotoxicity; decreased specific gravity, casts, proteinuria, or glucosuria should precede azotemia. When using amikacin, the author advises twice weekly urinalyses and blood panels assessing kidney factors. At the first sign of nephrotoxicity, amikacin administration should be discontinued; renal toxicity is generally reversible with early drug withdrawal. Aminoglycosides also have the potential to cause ototoxicity via induction of inner ear hair cell apoptosis and may result in permanent deafness although this is not commonly seen in the author’s experience.

**Prevention and the Future?**

While the future of MRS infections in animals and therapy remain a challenge, some insight can be gained regarding possible strategies for control and eradication from looking at experiences from countries that have achieved improvement and control of MRS infections in humans within their borders. The example most cited is Norway. While Norway did have reports of MRS infections decades ago, a proactive approach was taken to achieve control of the rapid increases in these resistant organisms and this approach has been met with some reasonable success. Norway had virtually eliminated MRS infections although some recent studies do show a slow upward trend in reported cases. But these rates are still dramatically lower than the rest of Europe and the US particularly. Norway instituted a program that included a dramatic reduction in the number of antibiotics dispensed to patients helping to slow resistance development of bacteria. In fact, many of the most potent and newer antibiotics are not registered for use in Norway as an added precaution. They also aggressively traced and isolated cases and quarantined documented cases until the infection was resolved. These relatively simple strategies resulted in marked control and provide insight into helping to control MRS infections in pets if adapted and promoted properly.
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Nosocomial infections are defined as any localised or systemic condition that occurs in a patient as a result of the presence of an infectious agent or its toxin that was not present or incubating at the time of hospital admission.¹ Nosocomial infections are of paramount significance within human medicine and are developing into an area of interest within veterinary medicine. The emergence of antibiotic resistance is a growing problem making prevention within both the human and veterinary hospital setting increasingly difficult. The emergence of such resistance emphasises the need to implement best practice preventative and control measures to reduce the acquisition of hospital acquired infections. Staphylococcus pseudintermedis and Staphylococcus aureus commonly colonise the skin, mucous membranes, urogenital tract and occasionally alimentary tract in dogs and humans.² Methicillin-resistant Staphylococcus pseudintermedius (MRSP) and methicillin-resistant Staphylococcus aureus (MRSA) have emerged as leading causes of hospital acquired infections in companion animals. Methicillin is a beta-lactam antibiotic that was widely used in the 1950’s. Methicillin had a good spectrum of resistance to beta-lactamase and therefore, was used to treat penicillin-resistant staphylococci. Shortly after its introduction, issues regarding resistance of bacteria to methicillin began to arise. Methicillin resistance is mediated by production of altered penicillin-binding protein (PBP2a) which is encoded by the mecA gene, prohibiting microbial binding of beta-lactam antibiotics.³

The existence of multidrug-resistant bacterial infections in veterinary hospitals has important occupational health implications. The prevalence of MRSA carriage by veterinarians is significantly higher than in the general population.³ Arguably, MRSA can be considered the most important nosocomial pathogen in human hospitals. The bi-directional transmission of MRSA between veterinary staff and companion animals has become an important occupational and nosocomial issue, as shown by a recent study reporting that MRSA is the second most prevalent nosocomial agent, associated with outbreaks in AVMA accredited veterinary teaching hospitals.⁴ Whilst most animals exposed to MRSA do not develop clinical disease; some become transiently colonised and most eliminate the pathogen. As with humans, colonised animals don’t typically show adverse effects unless risk factors allow for development of clinical infection. Once colonization has occurred, pets can transmit the pathogen to humans either directly or indirectly through fomites. Dogs may be carriers for at least six months after MRSP/MRSA acquisition and therefore constitute a potential cause for spread within the hospital and community.⁵ Previous antimicrobial therapy (especially fluoroquinolones and beta-lactams), immunosuppressive disease, surgery, use of invasive medical instrumentation and hospitalisation have been identified as risk factors for acquisition of nosocomial infections. Hospitalisation for more than three days has been associated with increased risk of acquiring MRSA.⁶ Dogs and cats are not believed to be a natural reservoir host for S. aureus, making it more likely that MRSA originates from a person than a pet.⁷

Expected baseline rates of healthcare-associated infections (HCAI) have not been established in the veterinary hospital setting. In a survey of 38 veterinary teaching hospitals at American Veterinary Medical Association accredited veterinary colleges, 82% of respondent hospital (31/38) recognised outbreaks of HCAI in the last 5 years, and 50% of hospitals identified zoonotic infections among personnel in the
previous 2 years. Without knowing the baseline rates of HCAI the number of infections that could have been prevented is unknown, therefore, targeting the areas for which require corrective action in terms of hospital infection control practices is complex.

An important aspect of MRSA and MRSP control is identification of potential sources of exposure. According to human medicine a significant proportion of hospital acquired infections (30-70%) can be prevented by proper compliance with infection control protocols. A number of strategies can be employed within veterinary hospitals to reduce the acquisition and transmission of nosocomial infections. Organisms are most commonly transferred between the hands of health care workers and patients. In turn, stringent hand hygiene protocols must be in place to limit nosocomial infection acquisition. There is growing awareness for the potential of fomites such as stethoscopes which can serve to spread antibiotic-resistant pathogenic bacteria. It has been demonstrated that stethoscopes can carry antibiotic-resistant pathogenic bacteria such as MRSA, and that both S. aureus and Enterococcus spp can survive on plastic surfaces for over 90 days. It is therefore essential that veterinary hospitals minimise infection transmission by the use of cleaning products such as isopropyl alcohol which effectively reduces the number of bacteria recovered from stethoscopes by 94-100%.

Otoscopes are used on a regular basis in veterinary hospital and can be vectors for spread of infection. Soaking cones in a sterile container of 2% chlorhexidine gluconate solution for 20 minutes has been shown to be effective in preventing growth of Pseudomonas aeruginosa organisms. Clothing worn by hospital personnel has also been implicated as a source of resistant pathogens and can result in re-contamination of hands following appropriate hand hygiene. Scrubs and white coats worn by hospital staff in human hospitals have been reported to be contaminated with multi-drug resistant bacteria in 4-20% cases. Not surprisingly, studies have shown that the location of maximal contamination occurs at the cuffs and pockets which are the areas of greatest hand contact. Using this knowledge, recommendations by the United Kingdom’s Department of Health have been made in an attempt to reduce the translocation of bacteria from clothing to hands include a “bare below the elbows” policy in which white coats, long sleeve shirts, jewellery and watches are not permitted in hospital staff.

Further studies have looked at the role in which the environment within a veterinary hospital plays, including indoor air in the secondary transmission of nosocomial Staphylococcus spp. Research has implicated aerosolised methicillin-resistant Staphylococcus spp (MRS) as the primary source of human surgical wound infections among patients with respiratory disorders and burns, and in health care workers in both human and veterinary health care settings.

High touch areas such as door handles, computer keyboards, and phones should be cleaned more frequently than other hospital surfaces. Several studies have demonstrated the persistence of bacteria and viruses on hospital fomites. By using plastic covers on phone headsets and keyboards, colonisation can be reduced.

There are currently no national standards for infection control programs in a veterinary hospital setting. This lack of standardisation is most likely attributable to the fact that most published recommendations for establishment of infectious control programs in veterinary hospitals have supported a customised approach. It is therefore imperative that veterinary healthcare workers ensure frequent hand sanitation and customise hospital infection control programs to reduce the acquisition of nosocomial infections.
References


A brief survey of bacteriology submissions from pyoderma cases seen in a dermatology referral practice in Queensland, 2006 – 2013

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Materials and Methods

A database search of practice records from 2006 to 2013 was undertaken to evaluate samples submitted for bacterial culture and sensitivity testing from dogs and cats with pyoderma. From the raw data the following records were excluded: samples with incomplete data or incomplete results, samples submitted from ears, samples submitted for fungal culture. The remaining results were examined but were not subjected to any statistical analyses.

Results

Using the 2006 sample submission rate (i.e. the overall number of bacterial culture and sensitivity samples submitted per new case examined) as a base of 1, a sample submission rate was calculated for subsequent years. This demonstrated an increase in yearly submission rates up to a maximum of 8 (relative to the 2006 rate) in 2012, before a reduction in the relative rate to 5.2 in 2013.

An examination of culture results on the basis of genus isolated demonstrated both an increase in the numbers of coagulase positive Staphylococci isolated up to 2012, which largely mirrored the increase in the rate of sample submission over the same period, and an increase in the numbers of different isolates reported.

There was only one submission (in 2013) that yielded a methicillin resistant Staphylococcus pseudintermedius (MRSP) during the period in question. One other case of MRSP (cultured from a sample submitted by the referring veterinary practice) was treated in the same year. To date, one further sample submission in 2014 has yielded MRSP.

The percentage of coagulase positive Staphylococcus isolates sensitive to various antibiotics during the period in question was as follows: enrofloxacin 81% (range 80-100%), clindamycin 55% (range 40-80%), co-amoxiclav 77% (range 70-95%), cephalaxin 78% (range 75-88%), trimethoprim / sulfamethoxazole 91% (range 87-100%), tetracycline 86% (range 80-100%), amoxicillin 14% (range 0-37%). There were no apparent trends toward change in the sensitivity data over the period. This data suggests that amoxicillin is not a good choice for treatment of superficial pyoderma in dogs and cats, and that cephalaxin and co-amoxiclav remain good choices.

Both of the MRSP isolates identified at the practice in 2013 and 2014 were susceptible to readily available oral antibiotics. MRSP does not, at the present time, appear to be a significant problem in veterinary dermatology referral practice in Queensland, but cases are seen, and therefore continued vigilance is warranted.
Prudent, evidence based use of antimicrobials – What does this mean for you?

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Abstract:

The global emergence of MRSP has emphasised the importance of appropriate antibiotic use in the veterinary industry. Implementing antimicrobial use guidelines into practice policies has been shown to increase antimicrobial stewardship and reduce the risk of antimicrobial resistance developing.

This presentation provides a brief summary comparing and contrasting the antimicrobial use guidelines provided by the FECAVA, BSAVA, BVA, AIDAP and the ISCAID for treatment of bacterial conditions with a focus on dermatological conditions.

Materials and Methods – The Veterinary Associations FECAVA, BVA, BSAVA, AVMA, AIDAP and ISCAID were explored for recommended antimicrobial use guidelines. A literature search using the following search terms was performed: antimicrobial, guidelines, prudent use, Staphylococcus pseudintermedius, pyoderma, resistance, culture and sensitivity.

Results – For the majority of components, all sources provide similar guidelines, although the specific emphasis varies.

All sources define culture and sensitivity (C+S) as necessary in any case of recurrent pyoderma, where rods are detected on cytology, or in deep pyoderma. Some elaborate further to suggest more explicit guidelines.

C+S testing is not mandatory in cases of superficial pyoderma, and the FECAVA suggest it may not be necessary as these cases often respond well to topical antiseptics. All sources (that explicitly differentiate between different severities of pyoderma) confirm that C+S is essential in cases of deep pyoderma. In addition to topical therapy, appropriate empirical therapy is recommended until C+S results are reported. C+S is not warranted in cases of otitis externa as the sensitivity results are not relevant in selection of topical agents due to the high concentration of medication achieved. Those sources that mention otitis media agree that treatment should be based on C+S results.

With respect to treatment the following recommendations are made:

- All sources agree that only topical therapy is required for surface bacterial overgrowth. Systemic antibiotic therapy is not justified in these cases. There are a wide variety of topical antiseptic recommendations depending on the source of the information. There is little evidence to suggest there is resistance of S. pseudintermedius to these agents, even multi-drug resistant strains, due to the high concentration of active ingredient available at the skin surface.

- Superficial pyoderma should be treated with topical antiseptics and empirical (first tier) systemic antibiotics may also be used in the first instance. Empirical therapy is regarded as acceptable by all sources in cases of uncomplicated pyoderma that are not recurrent, have only been treated with topical antimicrobials, or where there is no history of multiple antimicrobial treatment. The FECAVA suggest that systemic therapy may be unnecessary as many cases respond to topical therapy alone. Treatment should continue for seven days beyond clinical cure. If the condition becomes recurrent, C+S is required to guide subsequent antibiotic choices and does not automatically necessitate an elevation in tier of antibiotic required.
• Deep pyoderma demands immediate C+S testing. Topical applications are regarded as essential adjunctive treatment in combination with systemic antimicrobials based on C+S results. Systemic treatment should continue for 14 days beyond clinical cure.

• Cases of suspected MRSP/MRSA require appropriate hospital disinfection, essential topical antiseptic therapy and systemic antibiotics based on sensitivity testing.

Antibiotics are described as first, second or third line. First line antibiotics are those recommended for empirical usage. They are no less potent than second or third tier drugs when used in the right circumstances. Second line antibiotics are reserved for cases that did not respond to first line therapy, have been shown to be resistant to first line choices on sensitivity testing, or where client/patient factors prevent the use of a first line drug (eg. cefovecin). These include newer broad-spectrum drugs important to animal and human health where the development of resistance is of greater concern. All sources discourage the use of third line antibiotics usually reserved for use in life threatening infections in humans (vancomycin, imipenim etc). Prophylactic use of systemic antibiotics is also discouraged. ISCAID suggest that if pulse antibiotic therapy is considered, the case should be referred to a specialist.

Alternative treatment modalities for chronic recurrent disease, are briefly mentioned. Staph Phage Lysate and autogenous vaccine are possibilities but it is advised that further research is required in this area.

Appropriate recording of sensitivity patterns and outcomes post treatment are important as these provide trends for veterinary practices, to both determine suitable future treatments, and to monitor resistance in the local area. All sources strongly encourage client education to ensure compliance and understanding.

Conclusions - As the incidence of bacterial resistance is rising, immediate coordinated measures must be taken worldwide to ensure the lasting efficacy of the antimicrobials we have. No guidelines should be considered comprehensive and animal and client specific factors must be taken into account when determining an appropriate therapeutic plan.
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