CONCURRENT SESSION PRESENTATIONS

OTIC STRUCTURE AND FUNCTION

Cole LK
The Ohio State University, College of Veterinary Medicine, 601 Vernon Tharp Street, Columbus, Ohio 43210

Otitis refers to inflammation of the ear and may include not only the external ear canal in otitis externa, but may also involve the middle ear in otitis media, and the ear pinnae as well. Otitis externa is the most common ear disease in the dog and cat. The reported incidence is between 10 to 20% in the dog and 2 to 10% in the cat. Otitis externa is one of the most common reasons for animals to be referred to dermatology specialists, and is a very common clinical problem managed by general practitioners as well. It is important to be able to recognize normal otic anatomy to be able to diagnose otic disease.

Prior to examination of the animal, it is important to obtain a complete and thorough history from the owner. Even though this can be a time-consuming step, it is invaluable for a complete assessment of the animal and for insight into the primary cause of the otitis. A dermatologic history form can be mailed to the client prior to the appointment, or it can be filled out when the client arrives. Questions include:

- Onset of the otitis, unilateral or bilateral
- Seasonal, non-seasonal, or seasonally non-seasonal
- Current and previous treatment(s) used for the otitis as well as outcome, side effects, drug reactions
- Previous steroid administration
- Other dermatologic concerns: pruritus, alopecia, “rash”
- Current and previous diets and treats
- Current treatments for other concurrent diseases or preventive treatments (flea control, heartworm prevention)
- Any others in home with skin problems

One should also inquire about the clinical signs that prompted the owner to seek veterinary care. Common clinical signs associated with otitis externa include:

- Head shaking
- Scratching and rubbing the ears
- Pinnal alopecia
- Excoriations
- Odor
- Pain
- Hearing loss
- Behavioral changes

The next step is to perform a general examination as well as a dermatologic examination. In some cases, a neurological examination may be needed if one suspects the animal to have concurrent otitis media or otitis interna. If otitis media is present as well, the animal may exhibit neurological signs such as facial nerve paralysis or Horner’s syndrome. However, remember that the most common clinical sign of otitis media is recurrent otitis externa. Head tilting, circling, and nystagmus may indicate otitis interna.

EXTERNAL EAR CANAL

The external ear is composed of two elastic cartilages: the annular and auricular cartilage. The auricular cartilage expands to form the pinna. The pinna is a mobile structure designed to localize and collect sound waves and transmit them to the tympanic membrane. The auricular cartilage of the pinna becomes funnel shaped at the opening of the external ear canal.

The opening of the external ear canal is bounded by the helix (the free, slightly folded margin of cartilage at the base of the pinna) rostrally, the tragus laterally, and the antitragus caudally. The antitragus is a thin, elongated piece of cartilage caudal to the tragus, and separated from it by the intertragic incisure. This anatomical region is the area in which I will insert the otoscopic cone or otoendoscope into the ear canal for the otoscopic examination. The vertical ear canal runs for about 1 inch, extending ventrally and

slightly rostrally before taking a medial turn and forming the horizontal ear canal. There is a prominent cartilaginous ridge (“Noxon’s Ridge") that separates the vertical and horizontal ear canals and when the ear is in its normal position, makes otic examination of the horizontal ear canal difficult without elevating this ridge by grasping the ear pinna and lifting the ear.

The horizontal ear canal is composed of auricular and annular cartilage. The auricular cartilage rolls as it forms a tube. A separate cartilaginous band, the annular cartilage fits within the base of this tube. The annular cartilage overlaps with the osseous external acoustic meatus and articulates via ligamentous tissue, giving the external ear canal flexibility.

In most breeds of dogs, hairs are present in the external ear canal, decreasing in number from distal to proximal. A very few fine hairs are found at the entrance of the cartilaginous external acoustic meatus. I find these hairs are a useful landmark when flushing an ear to locate the tympanic membrane.

Cerumen is an emulsion that coats the ear canal. It is composed of desquamated keratinized squamous epithelial cells along with the secretions from the sebaceous and ceruminous glands of the ears. Cerumen from dogs with normal ears contains significantly more lipid than from dogs with otitic ears, although variation may occur in individual dogs. However, in dogs with otitis externa, those with high levels of lipids in their cerumen also had a high incidence of concurrent otic *Malassezia pachydermatis*. It appears that the overall lipid content and lipid class composition of human and canine cerumen are similar. In humans however, it is thought that cerumen protects the ear canal from invasion of microorganisms and injury and it exhibits bacteriocidal and antifungal activity, which may or may not be true in the dog.

The self-cleaning function of the external ear canal is primarily achieved by a process called epithelial migration. The epithelium in the ear canal grows outward from the tympanic membrane toward the opening of the external ear canal. These epithelial cells carry debris with them as well. When the anatomy of the epithelium of the ear canal is altered, or when the rate of epithelial movement is slowed due to age, debris accumulates in the ear canal or on the pars flaccida. This condition is termed “failure of epithelial migration”. Wax and keratin accumulate to form either soft wax plugs or ceruminoliths. Removal of these usually requires the patient to be under general anesthesia or heavily sedated. Soft wax plugs are usually easy to remove by flushing with a ceruminolytic agent and saline. However, ceruminoliths may be more difficult to remove, requiring additional soaking time with a ceruminolytic agent as well as the use of grasping forceps. After the removal of a ceruminolith, the tympanic membrane may appear abnormal, or may even have small tears in it. These small tears heal rapidly. If the tympanic membrane is torn while removing the ceruminolith, it is important to flush the ear with sterile saline to remove the ceruminolytic agent.

THE MIDDLE EAR

The middle ear consists of an air-filled tympanic cavity, three auditory ossicles, and the tympanic membrane. The tympanic membrane is located at a 45-degree angle in relation to the central axis of the horizontal part of the external ear canal. The tympanic membrane is a semitransparent membrane that separates the external ear canal from the middle ear, is thin in the center and thicker at the periphery, and is divided into two sections, the small upper pars flaccida and the larger lower pars tensa. The pars flaccida is the pink, small, loosely attached region forming the upper quadrant of the tympanic membrane that contains small blood vessels. In most dogs, grossly the pars flaccida is flat, while on occasion, in other dogs, this structure bulges into the external ear canal. This bulging pars flaccida can be present in the ears of normal dogs as well as in ears of dogs with otitis externa. Since no differences can be found histologically between a bulging pars flaccida and a flat pars flaccida, it appears unlikely that there is a structural difference causing the pars flaccida to bulge. There may be increased pressure in the middle ear of dogs with a bulging pars flaccida.

In the Cavalier King Charles spaniel, however, it does appear that a bulging pars flaccida is indicative of a middle ear disease, specifically primary secretory otitis media. Primary secretory otitis media (PSOM) or "glue ear" is a disease described almost exclusively in the Cavalier King Charles spaniel (CKCs). Dogs with this condition may exhibit head and neck pain, "air" scratching, neurological signs (facial paralysis, head tilt, vestibular signs), and hearing loss. In a retrospective review of 61 cases of PSOM, the diagnosis was made based on visualization of a bulging opaque tympanic membrane with an operating microscope and the finding of an accumulation of mucus in the middle ear after myringotomy. No additional tests were used to evaluate the dogs for otitis media.

The cause of the middle ear effusion is suspected to be due to Eustachian tube dysfunction, similar to children with secretory otitis media (SOM). SOM is one of the most common ear disease in children. Symptoms and signs are often lacking or may be minimal, such as mild hearing loss, which may not be recognized by the parents.

In my experience, radiography, specifically computed tomography (CT), is the best diagnostic test for a definitive diagnosis of PSOM. A bulging pars flaccida observed otoscopically in this breed is most likely indicative of PSOM. However, a normal tympanic membrane does not rule out the disease. Other diagnostic tests, such as hearing tests (brain stem auditory evoked responses [BAER]), impedance audiometry (tympanometry, acoustic reflex, pneumotoscopy), and bulla ultrasonography are currently being evaluated in a prospective study to determine their usefulness in the diagnosis of PSOM.

Current treatment of PSOM is removal of the mucus via a deep ear flushing of the middle ear. Culture and cytology of the mucoid exudate is usually negative; however, is still recommended. In the above retrospective study, various forms of medical management were used post-flushing, however, a number of CKCs did require repeated middle ear flushes to remove the mucus from the middle ear. This is not necessarily unexpected, since the cause of this disease has yet to be identified. The CKCs may develop an infectious otitis externa post-flushing.

It is important to be able to recognize and diagnose PSOM, since the clinical signs associated with this disease (head and neck pain, "air" scratching, neurological signs, deafness) are similar to some of the symptoms of other diseases recognized in the CKCs (syringomyelia, progressive hereditary deafness). Thus it is likely that some dogs with PSOM have been misdiagnosed with other diseases. PSOM is a treatable disease with a significantly more favorable prognosis than syringomyelia or progressive hereditary deafness. There may be a number of owners with CKCs that have this disease, but do not seek medical attention and diagnostics, thinking their CKCs has an "untreatable disease".

The pars tensa, the thin, tough, gray structure with radiating strands, occupies the remainder of the membrane. The pars tensa is attached to the osseous ring of the external acoustic meatus. The manubrium of the malleus attaches to the medial surface of the tympanic membrane. The outline of the manubrium of the malleus, the stria mallearis, may be visualized when the tympanic membrane is viewed externally. The pars tensa has a concave shape when viewed externally due to the tension applied by the manubrium of the malleus on the internal surface of the membrane. The point of greatest depression is called the umbo membrane tympani.

The tympanic cavity consists of a small epitympanic recess and a large ventral bulla. The tympanic bulla proper is adjacent to the tympanic membrane. In the dog, there is an incomplete bony septum or tympanic bulla ridge ("Rosychuk's Ridge"), which allows communication between the tympanic bulla proper and the ventral tympanic bulla. On the medial wall of the tympanic cavity, there is a bony eminence, the promontory, which houses the cochlea, and lies opposite the tympanic membrane. The cochlear (round) window is located on the caudolateral portion of the promontory. The cochlear window is covered by a thin membrane that oscillates to dissipate the vibratory energy of the perilymph in the scala tympani. The vestibular (oval) window lies on the dorsolateral surface of the promontory immediately adjacent to the pars flaccida. It is covered by a thin diaphragm. The footplate of the stapes is attached to the diaphragm over the vestibular window. Movement of the stapes against the vestibular window transmits movement to the perilymph within the vestibule of the osseous labyrinth. When flushing the middle ear, one must be very careful to avoid damaging the promontory or the round window, to avoid damaging the inner ear.

The middle ear cavity of the cat is different than the dog, and is divided by a septum into two separate tympanic cavities. In the small dorsolateral compartment lie the auditory ossicles, the osteum of the auditory tube, and the tympanic membrane. The larger ventromedial compartment is the air-filled

tympanic bulla. In order to remove exudate or a mass from the ventromedial compartment of the bulla, the bony septum would need to be perforated to gain entry. Rough handling of the bony septum may result in damage to the postganglionic sympathetic nerves. The nerves, which are visible submucosally as fine strands over the cochlear promontory, should be avoided during surgical removal of the septum in the cat.

The auditory tube is a short canal that extends from the nasopharynx to the rostral portion of the tympanic cavity proper. Its short bony wall is formed by the squamous part of the temporal bone rostrally and by the tympanic part of the temporal bone ventrally. It exits on the ventral aspect of the skull immediately rostral to the bulla and is protected ventrally by the sharp pointed muscular process of the temporal bone. The lateral wall is about 8 mm long and is nearly twice the length of the medial wall. The tube is oval in diameter and at its greatest diameter is 1.5 mm. It functions to equalize pressure on both sides of the tympanic membrane. The auditory tube is divided into three portions: cartilaginous (proximal and opens into the nasopharynx), junctional (part of tube at which the cartilaginous and osseous portions connect) and the osseous potion (distal and opens into the anterior middle ear). The osseous portion of the auditory tube is patent at all times while the cartilaginous potion is closed at rest and opens during swallowing. It is opened by the contraction of the levator muscle and tensor palatini muscle. The entrance to the auditory tube is obscured behind the soft palate, midway between the caudal aspect of the nares and the caudal border of the soft palate. Based on contrast-enhanced computed tomographic imaging, the auditory tube originates from the rostral, dorsomedial aspect of the bulla and exits the dorsolateral aspect of the nasopharynx just caudal to the hamulus process of the pterygoid bone.

The three auditory ossicles, the malleus, incus and stapes, are the bones that transmit and amplify air vibrations from the tympanic membrane to the inner ear. The malleus is attached to the tympanic membrane, the petrous temporal bone, and the incus. The incus is suspended between the malleus and the stapes. The footplate (base) of the stapes is attached to the vestibular (oval) window, which is in direct contact with the perilymph fluid. The vestibular window is approximately 18 to 20 times smaller in area than the tympanic membrane. When performing a myringotomy, the incision should be made into the caudoventral portion of the pars tensa to avoid damaging the ossicles.

NOTES

MANAGEMENT OF OTIC DISEASE

Cole LK
The Ohio State University, College of Veterinary Medicine, 601 Vernon Tharp Street, Columbus, Ohio 43210

The most frustrating cases of otitis externa are those that are chronic and recurrent. In order to manage the otitis, certain steps should be taken for a successful outcome. It is in these cases, that it is important not only to identify and treat any infectious agents present, but to also identify, treat and control the primary cause, any predisposing factors, as well as any additional perpetuating factors of the otitis.

STEP 1: Identify the primary cause of the otitis. Obtaining a complete history can aid you in compiling your differential list, in addition to your physical examination and otic examination. Primary causes of otitis externa include parasitic diseases, hypersensitivity disorders, foreign bodies, disorders of keratinization, juvenile cellulitis, autoimmune diseases, neoplasia, and polyps. These are the conditions or disorders that initiate the inflammatory process within the ear canal. In a retrospective study evaluating 100 dogs with acute (37%) and chronic-recurrent (63%) otitis externa, the most common primary cause of the otitis was due to allergic dermatitis (n=43 dogs). [1] On the other hand, in the cat, the most common causes of recurrent otitis externa are polyps and parasites (e.g. *Otodectes cynotis*).

STEP 2: Identify the predisposing factors of otitis. Predisposing factors facilitate the inflammation by permitting the external ear canal microenvironment to be altered allowing pathogenic or opportunistic bacteria to become established. These factors may include variation in ear conformation (pendulous pinnae, hair in the ear canal, congenital stenosis of the ear canal), moisture in the ear, and inappropriate prior therapies. Question the owner about previous treatments, the use of cotton-tipped applicators, or hair removal from the ears. It is important to eliminate as many of these factors as possible, realizing that some of these, such as ear conformation, cannot be changed.

STEP 3: Identify the perpetuating factors of otitis. Perpetuating factors sustain and aggravate the inflammatory process and prevent resolution or worsen an already present otitis externa. Bacterial and yeast infections, otitis media, and progressive pathologic changes are perpetuating factors of otitis externa, which need to be identified and controlled. The otic exam will allow you to assess the amount of exudates in the ear canals, estimate the amount of hyperplasia in the ear canals (along with palpation of the horizontal and vertical ear canals), and determine whether the tympanic membrane can be visualized or not. Based on your evaluation, decide if medical management is the best course of treatment for the patient. Otic cytology will establish if an infection is present in the ears, and will allow one to choose initial empiric topical otic therapy. A sample of the exudate smeared onto a slide with mineral oil can be performed to look for mites. The most common pathologic coccoid bacteria from dogs ear with otitis externa is *Staphylococcus pseudintermedius*, while the most common pathologic rod bacteria is *Pseudomonas aeruginosa*. If rod bacteria are detected cytologically, a bacterial culture and susceptibility (C/S) test can be performed to positively identify the organism. In patients with concurrent neurological abnormalities (e.g. facial paralysis, nystagmus, ataxia, head tilt), a neurological examination is indicated.

STEP 4: Treat the present otic infection with topical ear cleaning and drying agents, topical antimicrobial agents and topical glucocorticoids (if needed). If the ears are stenotic and hyperplastic, systemic glucocorticoids are indicated as well. Treat any other concurrent skin conditions (e.g. superficial bacterial pyoderma, yeast dermatitis).

Current ear cleaning and drying agents include:

1. DermaPet Malacetic Otic (DermaPet)
   Ingredients: Acetic acid, boric acid, surfactants
2. Epi-Otic Advanced (Virbac)
   Ingredients: Salicylic acid 0.2%, disodium EDTA, docusate sodium, PCMX, a monosaccharide complex (l-rhamnose, d-galactose, d-mannose)

3. Epi-Otic Cleanser (Virbac)
   Ingredients: Lactic acid and salicylic acid are present in encapsulated and free forms, chitosanide is present in encapsulated form, in docusate sodium and propylene glycol base
4. Ear Cleansing Solution (Vet Solutions)
   Ingredients: Deionized water, propylene glycol, aloe vera gel, SD alcohol 40-2, lactic acid, glycerin, dioctyl sodium sulfosuccinate, salicylic acid, fragrance, benzoic acid, benzyl alcohol.
5. Gent-L-Clens (Intervet/Schering-Plough)
   Ingredients: Lactic acid, salicylic acid in propylene glycol
6. Oti-Clens (Pfizer)
   Ingredients: Propylene glycol, malic acid, benzoic acid, salicylic acid
7. OtoCetic Solution (Vedco)
   Ingredients: 2% boric acid, 2% acetic acid, surfactants

Otic preparations that are ointment-based may not be as effective as those that are solution-based, if the ears are stenotic or hyperplastic, as may be the case in those patients with chronic otitis externa. Current topical antimicrobial agents for use in *chronic* ears based on cytologic and/or culture examination include:

Cytologic Examination: Coccoid bacteria and/or rod bacteria

A. Solution-vehicle topical
   1. Tresaderm (Merial)
      Ingredients: Thiabendazole, dexamethasone, **neomycin sulfate**

Cytologic Examination: Yeast organisms

A. Solution-vehicle topical
   1. Clotrimazole Solution (Vetoquinol)
      Ingredients**: Clotrimazole 1%,** propylene glycol, SD Alcohol 40, cocamidopropyl PG-dimonium chloride phosphate, chloroxylenol (PCMX), benzyl alcohol.
   2. Conofite Lotion (Intervet/Schering-Plough)
      Ingredients: **Miconazole nitrate 1%,** polyethylene glycol 400, and ethyl alcohol 55%.
   3. MalAcetic Ultra Otic (DermaPet)
      Ingredients: **Ketoconazole** 0.15%, acetic acid 1%, boric acid 2%, hydrocortisone 1%.
   4. Tresaderm (Merial)
      Ingredients: **Thiabendazole**, dexamethasone, neomycin sulfate
   5. TrizUltra (DermaPet)
      Ingredients: **Ketoconazole 0.15%**, tromethamine USP, edetate disodium dihydrate USP, buffered to pH8 with tromethamine HCL and deionized water.

Bacterial Culture: *Pseudomonas aeruginosa*

A. Pre-topical antibiotic flush
   1. TrizEDTA (DermaPet)
      Ingredients: Tromethamine USP, edetate disodium dihydrate USP, buffered to pH8 with tromethamine HCL and deionized water.
   2. Triz-EDTAChlor (DermaPet)
      Ingredients: Chlorhexidine 0.15%, tromethamine USP, edetate disodium dihydrate USP, buffered to pH8 with tromethamine HCL and deionized water.
B. Emulsion-vehicle topical
   1. Baytril Otic (Bayer Animal Health)
      Ingredients: **Enrofloxacin** 0.5%, **silver sulfadiazine** 1%.
C. Solution-vehicle topicals
   1. TobraDex Ophthalmic Solution (Alcon)

Ingredients: **Tobramycin**, dexamethasone

2. Tobrex Ophthalmic Solution (Alcon, less expensive generics available)
Ingredients: **Tobramycin**

C. Suspension-vehicle topical

1. Neomycin and polymyxin B sulfates and hydrocortisone otic suspension (generics)
Ingredients: Hydrocortisone 1%, neomycin sulfate, **polymyxin B sulfate**, propylene glycol, cetyl alcohol, polysorbate 80, purified water

D. Extra-label topicals

1. Injectable enrofloxacin (Baytril 2.27%) (Bayer Animal Health)
Formulation: 1 part inject able **enrofloxacin** mixed with 4 parts vehicle (e.g. Synotic, 1% hydrocortisone, saline)
2. Silver sulfadiazine (1% Silvadene cream) (Monarch Pharmaceuticals Inc)
Formulation: 1 part **silver sulfadiazine** cream mixed with 9 parts water
3. Injectable ticarcillin/clavulanic acid (Timentin) (GlaxoSmithKline)
Formulation: Add 26ml of saline to the 3.1 g bottle of **ticarcillin**/clavulanic acid to make a 100mg/ml concentration solution. Draw up 0.5 cc into 1 cc syringes, have owners freeze the syringes. Thaw when needed, good for 30 days.

STEP 5: Recheck the patient in three to four weeks to assess response to therapy, by performing an otic examination and otic cytology in addition to the general examination. This step is so critical to the management of otitis. If the patient is responding, initiate a food trial, if the otitis and pruritus (if present) is non-seasonal. In cases of seasonal otitis and pruritus, where other causes of the otitis and pruritus have been ruled out, a diagnosis of atopic dermatitis is made, and allergy testing or symptomatic therapy are initiated. If, however, the ears have not responded, then a deep ear flush should be scheduled, to clean the ears and evaluate the patient for concurrent otitis media. In dogs with recurrent ear infections of 6 months or longer, up to 82%of these dogs may have concurrent otitis media, with 70% having an intact but abnormal tympanic membrane.[2]

STEP 6: A short course (two to three weeks) of glucocorticoids should be utilized prior to the deep ear flush to decrease inflammation and stenosis of the horizontal and vertical ear canals. The deep ear flushing procedure is best done under general anesthesia in order to completely clean the ear. Once the animal is under anesthesia, radiographic imaging of the tympanic bulla is performed to stage the ear disease, remembering that normal radiographs do not rule out otitis media.[3] Next, the external ear canal is soaked for 10 minutes with a ceruminolytic ear cleaner. The ear is then flushed with warm sterile isotonic saline using a bulb syringe to remove large debris and exudate. This is followed by flushing with warm sterile isotonic saline using an 8 French polypropylene urinary catheter attached to a 12 cc syringe passed through an otoscopic cone. Once the ear is clean, the tympanic membrane is evaluated with an otoscope or video otoscope. If the tympanic membrane is not intact, cytology and bacterial C/S is performed from the middle ear cavity. This may be performed using the hand-held otoscope or the video otoscope. Using a hand-held otoscope, a sterile otoscopic cone is inserted into the horizontal ear canal and a sterile pediatric-size swab is passed into the middle ear cavity. The first swab is used for C/S. A second swab is passed into the middle ear for cytological analysis. If the video otoscope is used, an open-end 3 1/2 French Tom cat catheter attached to a 12 cc syringe is placed through the port of the otoendoscope. Saline is flushed into the middle ear cavity and aspirated back, the first sample for cytology, and the second sample for culture. Some ceruminolytic agents may be ototoxic. Therefore, the middle ear is flushed repeatedly with warm sterile isotonic saline using an open-end 3 1/2 tom cat catheter attached to a 12 cc syringe passed through an otoscopic cone or through the port on the otoendoscope to remove the ear cleaner.

If the tympanic membrane is intact, appears abnormal, and otitis media is suspected, a myringotomy is needed to obtain samples for cytology and bacterial C/S, and to flush the middle ear cavity. In the dog, an intact tympanic membrane does not rule out the possibility of otitis media.[2] Using a hand-held otoscope, a sterile otoscopic cone is inserted into the horizontal ear canal and the tympanic membrane is visualized. Using a sterile swab, an incision is made into the caudoventral quadrant of the tympanic membrane, specifically the pars tensa. The swab used for the myringotomy incision is submitted for bacterial C/S. A second swab is inserted into the original incision and the sample obtained

is used for cytological analysis. If the video otoscope is used to perform the myringotomy, an open-end 3 1/2 French Tom cat catheter is placed through the port of the otoendoscope, and the Tom cat catheter is used to make the incision. Saline is flushed into the middle ear cavity and aspirated back using a 12 cc syringe attached to the Tom cat catheter, and the first sample is for cytology, and the second sample is submitted for bacterial C/S. The normal tympanum heals in 21 to 35 days.[4] Therefore, if the ear is kept free of infection after the myringotomy procedure, the tympanic membrane should heal. Possible complications of ear flushing and myringotomy are Horner's syndrome, facial nerve paralysis, vestibular disturbances, and deafness. Owners should understand these complications and sign a consent form prior to the procedure.

After the otic flush, it is important that the patient is sent home on empiric topical and systemic therapy based on cytology, and the treatments may be modified once the cultures have been completed. Ototoxicity of most topical otic medications is not known, so if a myringotomy was performed,, owners should be instructed to watch for any signs of ototoxicity (facial nerve paralysis, Horner's syndrome, vestibular disturbances, deafness) and discontinue the otic medications if they occur. If the patient has non-seasonal otitis and pruritus, a food trial is commenced.

STEP 7: Recheck the patient three to four weeks after the ear flush to monitor the response to otic treatments as well as to the food trial (if it was indicated). In most cases of chronic otitis externa, where continual inflammation and stenosis have occurred along with increased cerumen production, which may alter epidermal migration, some type of maintenance otic therapy is required, such as a cleaning and drying agent, to keep the ear canal free of wax build up.

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NOTES

DIAGNOSTIC IMAGING OF THE CANINE AND FELINE EAR

Bischoff MG, DVM, MS, DACVR
VCA Aurora Animal Hospital
2600 W. Galena Blvd.
Aurora, IL 60506

I. The benefits of diagnostic imaging of ear disease are numerous; it is useful for identifying:
   a. The presence of unilateral or bilateral ear disease.
   b. The degree of middle or inner ear involvement.
   c. Peripheral versus central vestibular disease.
   d. Infectious or inflammatory versus neoplastic processes.
   e. Developmental abnormalities.
   f. Changes associated with chronicity.
   g. Involvement of adjacent structures.
   h. Post-surgical complications.

II. The main disadvantage of diagnostic imaging procedures is that anesthesia is necessary for optimum positioning.

III. Radiology
   a. Useful for evaluating the osseous tympanic bulla and external ear canals for chronic changes (mineralization or stenosis).
   b. When compared to surgical findings of 19 clinical cases of presumptive middle ear disease, false negative radiographic findings were found in 25% of the surgically confirmed cases of otitis media[1]. Therefore, radiographs are not considered a highly sensitive mode of diagnosing otitis media. In a study comparing CT and radiographic evaluation of otitis media, CT was determined to be more sensitive, but less specific than radiography[2].
   c. Radiographic views
      i. The lateral view is beneficial for evaluating the nasopharyngeal region and superimposed tympanic bullae.
      ii. The dorsoventral or ventrodorsal views allow a comparison of the tympanic bullae and external ear canals[1,3]. The dorsoventral radiograph provides greater ease in positioning and increased reproducibility[4].
      iii. The latero 20° ventral-laterodorsal oblique view is useful for visualization of the tympanic bulla with least superimposition of structures.
      iv. The rostro 30° ventral-caudodorsal open-mouth oblique view is the most valuable. This view allows direct comparison of both bullae with less soft tissue superimposition[1].
      v. The 10° ventrodorsal view is a supplemental view for felines[5]. It allows visualization of the tympanic bulla without superimposition of the occipital bone or the mandible.
   d. Normal radiographic appearance
      i. The bullae are thin-walled, gas filled bone structures with well-defined, smooth borders[6].
      ii. Must be careful not to mistake superimposed oral soft tissues for increased opacity in the tympanic bulla on the rostro 30° ventral-caudodorsal open mouth oblique radiograph.
      iii. Bilateral sclerosis of the tympanic bulla can be normal in older patients, but may also be a result of previous ear disease.
   e. Radiographic appearance of otic disease
      i. Otitis externa: The VD view is best for evaluating otitis externa[3].
         1. Stenosis and/or mineralization of the wall of the ear canal[3].
         2. Abnormal soft tissue opacity replacing gas in the external ear canal.

ii. Otitis media: The latero 20° ventral-laterodorsal oblique and rostro 30° ventral-caudodorsal open-mouth oblique radiographs are best for evaluating otitis media[3].
    1. Soft tissue opacity in the bulla[6].
    2. Sclerosis of the wall of the tympanic bullae or petrous temporal bone[6].
    3. Bony proliferation of the petrous temporal bone[6].
    4. Lysis of the tympanic bulla.
iii. Nasopharyngeal polyps: The latero 20° ventral-laterodorsal oblique and rostro 30° ventral-caudodorsal open-mouth oblique are most beneficial. The lateral view allows evaluation of the nasopharyngeal canal.
    1. Unilateral or bilateral increased soft tissue opacity within the tympanic bulla[3,6].
    2. Sclerosis of the osseous bulla[3,6].
    3. Signs of otitis externa and soft tissue opacity in the horizontal ear canal.
    4. Increased soft tissue opacity in the nasopharyngeal region[3].
iv. Neoplasia
    1. Similar signs to otitis media: soft tissue opacity within the tympanic bulla, sclerosis and/or lysis of the osseous bulla[3,6].
    2. Soft tissue mass effect around the external ear canal with impingement or obliteration of the external ear canal.
    3. Aggressive neoplasms (squamous cell carcinoma, mucinous gland adenocarcinoma) can result in lysis of the adjacent calvaria[3].
v. Miscellaneous
    1. Craniomandibular osteopathy causes bilateral sclerosis of the osseous tympanic bullae[6].
    2. Head trauma can cause fracture lines (radiolucencies) [6].
    3. After bulla osteotomy, the bullae may not completely reform post-surgery, but satisfactory clinical outcome was seen with either partial or complete reformation[7].

f. Canalography is used to determine if the tympanic membrane is ruptured (in 14% of cases a ruptured tympanic membrane may appear intact otoscopically)[8].
    i. Ventrodorsal or dorsoventral and rostro 30° ventral-caudodorsal open-mouth oblique survey radiographs.
    ii. Non-ionic water soluble positive contrast medium such as Iohexol has been used with no adverse effects[8-9]. This can be used undiluted or diluted with an equal amount of sterile saline.
    iii. With a tomcat catheter, 1 ml of positive contrast medium is administered into the external ear canal and the canal is massaged. Additional contrast is added to the level of the tragus[9]. Plug ear with cotton to prevent artifacts[8].
    iv. Ventrodorsal, latero 20° ventral-laterodorsal oblique and rostro 30° ventral-caudodorsal open mouth oblique radiographs post-contrast medium administration. Flush ears with saline following procedure.
    v. Subtle bulla opacification may be seen on the rostrocaudal open-mouth view[8].
    vi. A stenotic ear canal has a proximal to distal annular cartilage diameter ratio of less than 0.65[9].
g. Fistuology is used to evaluate fistulous tracts, which may be a complication of TECA[10].
    i. Lateral, dorsoventral, latero 20° ventral-laterodorsal oblique, and rostro 30° ventral-caudodorsal open-mouth survey radiographs.
    ii. 1-2 ml of non-ionic water soluble positive contrast medium, such as Iohexol, can be administered into the fistulous tract using a tomcat catheter. Repeat radiographic views.

IV. Computed Tomography (CT)

a. Useful for evaluation of otitis media, nasopharyngeal polyps, unilateral or bilateral otitis externa, extent of neoplasia, and assessing communication of fistulous tracts and abscesses with the external ear canal.
b. CT has the same interpretive principles used for radiography, but uses cross-sectional imaging with less superimposition of structures.
c. Technique
    i. 1 to 3 mm contiguous transverse images made from just rostral to the tympanic bulla to just caudal to the petrous temporal bone[2,6,11].
    ii. Contrast medium administration is not typically necessary in uncomplicated cases of otitis media. It is used if neoplasia or otitis interna are suspected[6].
    iii. View at both bone and soft tissue windows
        1. Bone - window width of 2300 and window level of 200.
        2. Soft tissue - window width of 400-500 and window level of 40-50.
        3. If the bulla are fluid filled, evaluate at window width > 2000[12].
d. Normal CT appearance
    i. Osseous bullae should appear symmetric with thin, well-defined walls.
    ii. Lumina of the tympanic bulla and the external ear canals should be of gas density.
    iii. External ear canal is uniform in thickness without luminal narrowing or obstruction.
    iv. Cochlea of inner ear should be visible with thin slices using conventional CT.
e. CT appearance of otic disease
    i. Otitis externa may demonstrate mineralization and/or narrowing of the external ear canal with or without soft tissue density material within the lumen.
    ii. Otitis media can cause osteolysis and/or thickening/irregularity of the wall of the osseos bulla. Additionally, there may be soft tissue density representing fluid or tissue within the tympanic cavity.
    iii. Otitis interna is difficult to assess using CT unless there is severe destruction of the inner ear[13]. This may be evaluated better with MRI.
    iv. Nasopharyngeal polyps may appear as soft tissue density structure(s) extending from the middle ear into the lumen of the external ear canal[14]. Alternatively, polyps may appear as a soft tissue density mass in the nasopharyngeal region with concurrent soft tissue density within the tympanic bulla. Thickening of the osseous bulla may also be present. Factors which may help differentiate a polyp from neoplasia include the age of the patient, presence of soft tissue structure in the nasopharyngeal region, and lack of a mass effect external to the tympanic bulla or external ear canal. Sagittal and parasagittal reconstruction images may be helpful.
    v. Neoplasia demonstrates a soft tissue mass effect with involvement of the external ear canal and/or tympanic bulla. Osteolysis of the tympanic bulla, petrous temporal bone, and/or adjacent calvarium may also be present. Contrast medium is administered to better evaluate the extent of soft tissue and/or inner ear involvement.
f. Miscellaneous
    i. Abscessation as a post-surgical complication can be seen as areas of hypodensity at the surgical site with peripheral contrast enhancement.
    ii. Fistulous tracts can appear as focal areas of gas extending outside the ear canal. Contrast medium may also be administered into the fistulous tract with repeated scanning to determine the extent.

V. Magnetic Resonance Imaging (MRI)

a. Superior soft tissue contrast and multiplanar imaging are advantages of MRI[15]. It is useful for differentiating central versus peripheral vestibular disease[16].
b. Limitations of MRI include availability, cost, and anesthesia time.
c. Technique: Standard MRI protocol includes transverse images (T1- weighted pre- and post-contrast, T2-weighted and proton density weighted), as well as sagittal/parasagittal and/or dorsal T1-weighted images made post-contrast medium administration[17]. Additionally, dorsal T2-weighted images have been suggested for cats[18].

d. Normal MRI appearance: Signal void (black) produced by the osseous tympanic bullae cannot be differentiated from the gas (black) in the tympanic cavity and external ear canal.
e. MRI appearance of otic disease
    i. Otitis externa appears as narrowing of the external canal with increased signal intensity and thickening of the canal wall on T1- and T2- weighted images[19]. There may be hyperintense thickening of the tympanic membrane[19]. Fibrous tissue or exudate produces signal intensity within the lumen of the ear canal. Mineralization of the external ear canal produces signal void, which can be difficult to differentiate from the normal auricular cartilage unless changes are severe.
    ii. Otitis media: Contents of the tympanic cavity can appear hyperintense on T2-weighted images. This can appear as medium signal intensity on T1-weighted images, with enhancement of the lining of the tympanic bulla post-contrast administration[13]. However, there may be a laminated appearance of high and low signal intensities of the mucosa of the tympanic bulla on T2-weighted images where hypointense areas represent fibrous tissue associated with chronic disease[19]. Osseous changes will be difficult to assess on MRI, especially when mild.
    iii. Otitis interna: There is a lack of signal intensity from the intra-labryinthine fluid on T2-weighted images, which may represent replacement of fluid with fibrous tissue[13]. Secondary meningeal enhancement medial to the inner ear may be seen on T1-weighted post-contrast images[20].
    iv. Nasopharyngeal polyps: Can cause strong contrast enhancement of the polyp on T1-weighted images, and possibly nonuniform hyperintensity of the polyp on T2-weighted images[18].
    v. Neoplasia can cause osteolysis of the tympanic bulla, petrous temporal bone and/or local invasion of adjacent structures[13]. Malignant melanoma within the tympanic bulla has been described without osteolysis or contrast enhancement[18].
f. Brain abscessation can occur secondary to otitis interna/media. A ring enhancing lesion (focal hypointensity centrally with a mildly hyperintense rim on pre-contrast T1-weighted images) may be seen adjacent to the inner ear/tympanic bulla in later stages of abscess formation[21]. This may have a mixed signal intensity on T2-weighted images. Abscessation may be seen in association with otitis interna/media, which may help differentiate it from neoplasia, encephalitis, and hemorrhage.

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NOTES

GETTING THE MOST OUT OF YOUR SKIN BIOPSIES

Affolter VK
UC Davis, School of Veterinary Medicine, Dept. of Pathology, Microbiology, Immunology, Davis, CA USA

INTRODUCTION

Pathologists always interpret the histological features in the context with the gross appearance of the lesions. As dermatopathologists and dermatologists we actually look at the same lesions. We are fortunate to have the lesions readily visible on the surface of the patient and should take advantage of this situation. The keyword to "getting the most out of a biopsy" is: TEAM WORK!! The pathologist often has to rely on the clinician's exact description of the lesions observed on the patient - as submitted samples (usually punch biopsies) are too small to reflect the gross appearance of the lesion.

WHEN IS A BIOPSY NECESSARY / HELPFUL

A biopsy is a powerful diagnostic tool, if cases are chosen appropriately. With very chronic hyperplastic lesions the biopsy often is not diagnostic. However, it may at least help to rule out certain diseases. For a biopsy to be helpful, it is important that samples are taken early during the disease process and - if ever possible - primary skin lesions are chosen. Biopsies should always been considered if: a) unusual skin lesions are observed, b) lesions do not respond to treatment *example: pustular disease, which does not respond to antibiotics* and c) if a neoplastic disease has to be considered *example: erythroderma due to pagetoid form of epitheliotropic lymphoma in older dogs*

CHOOSE BIOPSY SITES

a. Representative lesions: The most important factor is the identification of representative lesions. A careful screen for and sampling of primary skin lesions increases the likelihood of an etiological diagnosis. *Example: fresh pustules, vesicles and papules are more rewarding than a deep chronic ulcer.*

b. Marking of biopsy site: It is helpful to actually mark the biopsy site as lesions may change after sedation and in particular after local anesthesia.

BIOPSY TECHNIQUE

a. Number of biopsies: If various lesions are observed, they should be represented by taking several biopsies. This will assist the pathologists to evaluate for: 1) evolution of lesions, 2) potential of two separate disease processes. It is not unusual that given several different biopsies, only one may reveal the diagnostic features.

b. Do not disturb the biopsy site: It is absolutely crucial to NOT disturb the surface of the skin lesions. Hence, by NO MEANS scrub, shave and disinfect the skin surface, as it will remove valuable information. Crusts represent the history of what happened to this skin area earlier and may be crucial to achieve an etiological diagnosis. It is not unusual that we find diagnostic lesions in the crusts, but no longer in the epidermis or dermis; *example: rafts of acantholytic cells may still be present in the crusts, whereas active stages of keratin dissociation may no longer be present. It will be the crust, which assists in diagnosing pemphigus foliaceus.*

c. Preparation of biopsy site: Carefully clip the hair coat without disturbing crusts and surface lesions. Do not disinfect the skin surface, unless the biopsy is used for culture. The biopsy site can be disinfected after removal of the sample and prior to closure of the biopsy site.

d. Local anesthetic: It is important to inject the local anesthetic strictly subcutaneously, as intradermal injection will result in marked artifacts of the biopsy site.

e. Punch biopsy versus wedge biopsy: In most instances punch biopsies are the technique of choice. If several biopsies are taken – the punches should only be reused as long as they remain sharp and are cutting the skin surface well. Dull biopsy punches will induce marginal artifacts. Tissues shrink upon formalin fixation; therefore punch biopsies smaller than 6mm should be avoided, except for very delicate locations such as the nasal planum, ear margins or close proximity to eyelids and foot pads. For most instances punch biopsies should be taken from the center of the lesions; they are bisected for pathology processing and if they are taken at the margin, half of the biopsy may not reveal pathologic features. However, in particular with expanding skin lesions, lesional margins may offer early features of the disease process, whereas central lesions may reveal mostly chronic morphologic changes. Such an event may best be represented with a wedge biopsy (see below). Alternatively, punch biopsies can be taken from the center as well as from the margin of the lesion and labeled as such. Deep (subcutaneous) lesions may be difficult to samples with punch biopsies. To sample deeper tissues, it may be helpful to take an 8mm punch biopsy first, followed by a 6mm punch taken through the primary biopsy site. Wedge biopsies are most suitable to sample 1) large solitary lesions, as they can be removed entirely and margins can be evaluated (*example: suspected neoplastic lesions*), 2) intact vesicles and pustules, as biopsy punches may disrupt these lesions, 3) deep pannicular lesions, and 4) ulcerated lesions, as it allows to sample the lesional margin as well as the actual ulcer.

f. Biopsy samples have to be handled carefully. Avoid pinching of the samples while removing them. Blotting the skin samples carefully on a piece of gauze assists to remove blood on the surface. However, leaving biopsies uncovered on a dry piece of gauze for a prolonged period of time must be avoided; the samples dries out, which interferes with evaluation of the biopsies. *Punch biopsies*: after blotting they are immersed immediately in formaldehyde for fixation (see below). Alternatively they are wrapped in saline dampened gauze if submitted as fresh tissue (see below). *Wedge biopsies*: large scalpel biopsies have the tendency to role once immersed in formalin. To keep the sample flat while fixing, it can be placed on a piece of cardboard or wooden spatula (subcutis down). The sample is then emerging in formalin with the skin facing down.

g. DO NOT …. i) …use cauters to remove punch biopsies or small wedge biopsies; it induces coagulation of the tissue, which interferes with interpretation of the histology; ii) …pinch the skin sample with forceps, it induced major crush artifact

h. Separation of samples: if different skin lesions are sampled, they should be submitted separately with exact indication of the location they have been taken from.

HANDLING OF TISSUES FOR SPECIFIC TECHNIQUES

a. Fixed samples: 10% buffered saline should be used (ratio tissue sample to formalin should be at least 1:10). Formalin fixed samples are embedded in paraffin and 5µm sections are stained with hematoxylin & eosine and used for routine morphologic evaluation. Formalin-fixed tissue can also be used for:
   i) Most special stains (infectious pathogens etc).
   ii) Immunohistology with antibodies suitable for formalin-fixed tissues
   iii) Clonality testing (T cell receptor gamma: TCRG; immunoglobuline heavy chain: IgH; kappa deleting element: KDE)
   iv) Polymerase chain reactions for infectious pathogens
   v) Reprocessing for electron microscopy is possible after fixation in formaldehyde. If samples are taken for EM directly - pathologists should be contacted to get a sample f fixative (2.5% glutaraldehyde in 0.1M sodium cacodylate buffer)

b. Fresh samples: the samples are wrapped in saline dampened gauze and placed in a plastic container or ziplock bag. The samples need to be kept cool (+4^{o}C). They need to be kept separate form formalin samples as fumes of formaldehyde may have enough influence on fresh tissues to interfere with successful immunohistochemistry on fresh, snap-frozen tissues with certain antibodies, which do not work in formalin-fixed tissues.

c. Impression preparations: This is most applicable for neoplastic lesions. Before immersing a sample into formalin, it can be bisected; the cut surface can be blotted to remove oozing blood and then slightly pressed against the glass slides. The slides are subsequently air-dried and kept in the refrigerator (+4°C) in a box with a dessicator. These slides can be used for immuohistochemistry (same as fresh, snap frozen tissues).
d. Aspirates – smears: same as impression preparations!
e. Samples fro RNA evaluations: RNA degrades very rapidly after tissue collection. Very small samples have to be immersed immediately into RNAlater-solution and then kept at +4°C.

SUBMISSION

Many laboratories have specialized forms for skin biopsy submissions; the forms contain: a list of skin lesions and a schematic of a dog / cat (dorsal and ventral aspect), so location of lesions can be indicated. Each submission needs to include the following information:

a) Complete signalment: Breed, age and sex. Some breeds are predisposed for certain diseases
b) A complete clinical history: including
   i. Complete list of clinical signs
   ii. Complete list of skin lesions and their locations
   iii. Previous treatments (systemic and topical): dosage, duration and response to it. Time since treatment has been stopped (important in particular for corticosteroids). This list of treatments should also include medication for any other condition in this patient as well as supplements and preventative substances (vaccines, heartworm prevention etc.)
   iv. To add pictures of the skin lesions is tremendously helpful
   v. Presence or absence of pruritus
c) Results from blood work
d) Performed diagnostic tests preformed: scrapings, cultures (fungal and bacterial ±sensitivity tests), diets, endocrine tests,
e) List of clinical differential diagnoses: this is important. Often in the context of ruling out a certain disease.

If possible submit your biopsies to a dermatopathologist. Interpretation of skin pathology beyond a purely morphologic diagnosis requires a good understanding of clinical dermatology. In the majority of cases the histological changes can only indicate an etiological diagnosis when interpreted in association with the clinical lesions.

INTERPRETATION OF PATHOLOGY REPORT

Most pathology reports contain the following sections:

a. Description of the histopathological features seen on the samples submitted; this section may include features seen with special stains. It is important that clinicians read this description, to educate themselves about how histological changes relate to their clinical impression. Dermatologists learn to interpret the histological features in the context of the clinical signs.
b. Morphologic diagnosis summarizes the features in the histological description. This may include very specific features, which already indicate the etiology.
c. Etiological diagnosis / disease: this is often listed in the context with the morphological diagnosis - often connected with "consistent with…" or "suggestive of .."- if features seen on the glass slides are diagnostic for a specific disease. *Example: demodicosis as mites are seen within the hair follicles*
d. Comments: This is often the most important section. The dermatopathologist tries to put the histopathological findings into the context of the clinical history and the lesions presented in the samples submission. Often this will result in listing differential diagnoses, which then need to be followed up on by the clinician. This section is also used to refer to questions from the clinicians and to refer to the differential diagnoses listed by the clinician. *Examples: there is no evidence for endocrine induced alopecia in the samples submitted.* The pathologists also may list additional techniques that may assist to achieve an etiological diagnosis. *Example: Immunohistochemistry, clonality testing, polymerase chain reaction etc.*

“PULLING ALL THE DATA TOGETHER!”\
It is most important that both clinicians and pathologists are working as a team. This means that pathologists reading skin biopsies, have to know how skin lesions present clinically and clinicians have to understand the description offered on the pathology report. With an excellent history and description of the clinical lesions the pathologists will often be able to give a more distinct list of possible differential diagnosis based on the histopathological features. And with a correct morphological diagnosis and comment on the pathology report, the clinician should be able to come up with a shortlist of differential diagnosis. Both pathologists and clinician should communicate if pathologic findings and clinical description do not “fit together”. Remember: IT IS TEAMWORK!!!!

NOTES

EQUINE DERMATOLOGY: BEGINNINGS AND RECENT CLINICOPATHOLOGICAL DABBLINGS

Scott, DW
College of Veterinary Medicine, Cornell University, Ithaca, NY 14853

When I entered the arena of clinical dermatology in 1971, my equine dermatological "Bible" was the classic textbook — Veterinary and Comparative Dermatology — written by Drs. Frank Král and Robert Schwartzman, and published in 1964.[1] This textbook contained descriptions of 80 distinct equine disorders with dermatological manifestations. Among these were, "summer eczema" (today's insect-bite hypersensitivity and atopic dermatitis), "neurofibromas and fibrosarcomas" (the photographs, almost certainly depict today's sarcoid), "keloids" (today's exuberant granulation tissue), "acquired hypertrichosis" (today's pituitary pars intermedia dysfunction), and "scratches/grease heel" (today's multifactorial pastern reaction pattern).

Three major driving forces in equine dermatology surfaced in the 1970s: Dr. Tony Stannard (California, USA),[2] Dr. Reg Pascoe (Queensland, Australia),[3] and Dr. Bill McMullan (Texas, USA).[4] Thanks in large part to the influence of these three individuals, the number of recognized equine cutaneous disorders had almost tripled to 239 by 2003.[5] Most of this knowledge explosion was fired by improved clinical observation, laboratory techniques (e.g., dermatohistopathology), and therapeutic protocols.

MULTINUCLEATED HISTIOCYTIC GIANT CELLS

Skin-biopsy specimens from 335 horses with inflammatory dermatoses and from 27 horses with normal skin were evaluated for the prevalence, number, and morphological types of multinucleated histiocytic giant cells (MHGC).[6] The prevalence and number of MHGC were greater in granulomatous than in nongranulomatous dermatoses. Infectious and noninfectious dermatoses were not different in terms of prevalence, number, and morphological types of MHGC. Foreign-body MHGC were the predominant type in almost all cases. MHGC were not seen in normal skin.

MHGC are frequently present in a wide variety of inflammatory dermatoses in the horse. Because the prevalence, number, and morphological types of MHGC are of minimal diagnostic significance, special stains and tissue cultures are often necessary to confirm specific diagnoses.

INFILTRATIVE LYMPHOCYTIC MURAL FOLLICULITIS

Skin-biopsy specimens from 250 horses with inflammatory dermatoses and from 27 horses with normal skin were evaluated for the prevalence of infiltrative lymphocytic mural folliculitis (ILMF).[7] ILMF was present in 82% of the diseased skin specimens examined. ILMF was not seen in normal skin.

It appears that ILMF is frequently seen in a wide variety of equine inflammatory dermatoses and, therefore, is of little diagnostic significance. However, ILMF is not seen in normal skin and the presence of lymphocytes in equine hair follicle epithelium should, therefore, be considered abnormal.

CUTANEOUS "EOSINOPHILIC GRANULOMAS" ASSOICATED WITH COAGULASE-POSITIVE STAPHYLOCOCCAL INFECTION

Two horses were presented for steroid-resistant "eosinophilic granulomas". Clinical presentations were not typical for the classic eosinophilic granuloma.[5] Histopathological findings included diffuse eosinophilic granulomatous inflammation with multifocal areas of collagen flame figures and necrosis. Throughout the inflammation were small, multifocal areas of neutrophil accumulation. Special stains were negative for fungi and bacteria. Tissue cultures were positive for coagulase-positive staphylococci.

Both horses were cured with a five-day course of dexamethasone (0.1 mg/kg PO q24h) and a four-week course of trimethoprim-sulfamethazole (15 mg/kg PO q12h).

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NOTES

HORSES AND THE RISK OF ZOONOTIC INFECTIONS

Jeff B. Bender, DVM, MS [a,] *, Dean T. Tsukayama, MD [b]

[a] University of Minnesota, 136F ABLMS, 1354 Eckles Avenue, St. Paul, MN 55108, USA [b] Department of Medicine, Hennepin County Medical Center, 701 Park Avenue South, Minneapolis, MN 55417, USA

Zoonoses are those diseases that are shared in nature by human beings and vertebrate animals [1,2]. A more stringent definition identifies those diseases that are transmitted from vertebrate animals to human beings [1]. In the latter definition, there are relatively few diseases that are transmitted directly from horses to people. However, greater public attention has been focused on the broad group of emerging zoonoses, such as severe acute respiratory syndrome (SARS), influenza, bovine spongiform encephalopathy (BSE), and monkey pox. Likely emerging zoonotic agents like these will continue to increase in frequency with the encroachment of human populations on areas not commonly frequented by people and by rapid and widespread international movement of human beings and animals. Recently, the Institute of Medicine acknowledged that many microbes have apparent harmony with animals but are pathogenic to human beings [3]. The increasing recognition of emerging diseases is attributed to many factors, including worldwide trade, mass movement of people for leisure or work, increasing urbanization (ie, daycare facilities, prisons, homeless shelters), environmental changes, resource consumption, demographic changes like aging, and increasing numbers of immunocompromised patients. In addition, most emerging infectious diseases are considered zoonotic, and this report recommended the need for an interdisciplinary approach from a broad range of disciplines, including veterinary medicine, to address this phenomenon.

The focus of this article is on horses and the risk of zoonotic infections, especially in the hospital setting. There is a need to identify potential nosocomial and zoonotic disease events rapidly, with the purpose of preventing employee, owner, and animal illness. Also, in the context of emerging diseases, veterinary hospitals can provide a unique surveillance nidus to detect unusual disease events in animals and their owners. This is not an inclusive discussion of all diseases shared between horses and people but a synopsis of recent diseases of concern and the challenges they present. The following discussion includes (1) new and deadly agents, (2) old diseases that have resurfaced, (3) disease challenges that consume resources and energy, (4) diseases with complex webs of transmission, and (5) potential problems for immunocompromised human beings. A brief discussion of modes of disease transmission and infection control strategies is also highlighted from the human hospital perspective.

New and deadly agents

Horses are not immune to emerging diseases, many of which are zoonotic. Recently identified emerging diseases in horses include equine protozoal myeloencephalitis, clostridial enterocolitis, ehrlichiosis, Japanese encephalitis, vesicular stomatitis virus infection, Venezuelan equine encephalomyelitis (VEE), Hendra virus infections, and West Nile virus encephalitis. Viruses common to people and horses include rabies, influenza, vesicular stomatitis virus, Japanese B encephalitis virus, and a number of alpha viruses. Mosquitoes can carry Eastern equine encephalitis, Western equine encephalitis, VEE, and West Nile virus from birds to horses and people (Table 1). The likely bird source and mosquito vector may vary for each virus. Generally, neither horses nor people seem to be a significant source of transmission of these infections but are instead terminal hosts. The exception is VEE, in which horses can develop sufficient viremia to serve as amplifiers of the virus. Rare cases of VEE have been linked to inhalation of the virus in laboratory settings [2]. Direct transmission from horses to people in a veterinary setting is unlikely.

* Corresponding author.
E-mail address: bende002@umn.edu (J.B. Bender).

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The reality of emerging diseases and the potential impact on human and equine health was exemplified by the death of horses and people in Australia in 1994. This outbreak of severe respiratory disease affected 18 horses, their trainer, and a stablehand in Queensland, Australia [4]. Additionally, a 35year-old man developed a brief episode of aseptic meningitis in August of 1994 after caring for two ill horses [5,6]. He survived this initial infection but developed severe encephalitis resulting in death 13 months later. The 35year-old patient assisted in necropsies of affected horses without gloves, a mask, or protective eyewear and likely had close contact with ill horses. Since 1994, there have been two other outbreaks recorded in horses. Three human cases have been attributed to these outbreaks. The level of contagiousness of Hendra virus is likely minimal, as evidenced by the identification of only small and infrequent outbreaks detected since 1994 and the lack of seroconversion in a large number of people and horses tested in Australia [7,8]. These scenarios highlight new challenges that can affect horses and their human caretakers. The identified agent, the Hendra virus, is likely transmitted by direct contact with respiratory secretions of infected animals. Fruit bats (*Pteropus* sp) are the likely reservoirs.

New diseases are likely to be ongoing challenges in the future. These challenges require the clinician's awareness of new or unusual disease presentations and an awareness of measures to take when unusual cases are encountered. Also, this requires us to teach our veterinary students and technicians about basic infection control measures, including standard and transmission-based precautions. Standard precautions apply to all patients and stipulate that gloves should be worn to touch any of the following: blood, body fluids, secretions (except sweat), nonintact skin, and mucous membranes. Transmission-based precautions apply to disease-specific modes of transmission, such as contact precautions applied to a horse with dermatophytosis or droplet precautions applied to a horse with rabies. These human terms can be applied and modified to the emerging science of infection control in veterinary medicine.

Disease	Geographic distribution	Age group affected	Human mortality (%)	Neurologic sequelae (human)	Equine mortality (%)
Eastern equine encephalitis	West, Midwest East, Gulf	Children	50–75	80% of survivors low	70–90
La Crosse encephalitis	Coast, South	Children	\1	—	—
St. Louis encephalitis	Central, West, South	Adults (>50 y)	2–20	20% of survivors	—
Venezuelan equine encephalitis	South	Adults	1	Rare	30–80
Western equine encephalitis	Central, East	Infants and Adults (>50 y)	5–15	Moderate in infants, otherwise low	20–50
West Nile encephalitis	Across North America	Adults (>50 y)	10	Rare, acute flaccid paralysis syndrome	30

Table 1
Characteristics of North American arboviral encephalitides in human beings
Abbreviation: y, years.

Old threats become new

Some diseases have long been forgotten in developed countries because of improved management and the advent of antimicrobials; however, some of these diseases may still pose significant threats. This was highlighted by the diagnosis of *Burkholderia mallei* infection (glanders) in a military researcher in March of 2000 [9]. The last reported case of naturally acquired glanders in the United States was in 1945, and the most recent case demonstrated the difficulty of recognizing ''nearly forgotten'' diseases. The concern for these diseases is the potential they pose as engineered pathogens for terrorism. Some researchers suspect that strains of antimicrobial-resistant B *mallei* have already been produced. B *mallei* is currently endemic in Africa, Asia, the Middle East, and Central and South America and is known to cause infection in horses, mules, donkeys, sheep, goats, pigs, and human beings. It is traditionally transmitted by direct contact with infected animals. Other means of transmission include ingestion and inhalation, especially with the development of bioengineered strains, which were developed for warfare purposes. Clinical presentation varies by mode of transmission. Case fatality may be greater than 50% if untreated. Standard precautions are necessary to prevent transmission.

Horses, mules, and donkeys are most susceptible to illness; currently, there is no effective treatment [10]. There are four forms of infection: localized cutaneous infection of the skin or soft tissue; pneumonitis; sepsis; or a chronic form resulting in multiple abscesses of the liver, spleen, skin, or muscle. Disease control involves slaughter of ill and carrier animals. In human beings, the disease is manifested as pustular skin lesions or pulmonary disease after an incubation period that ranges from days to several weeks. The portal of entry is the skin or lungs. Regional adenopathy and systemic symptoms, such as fever and malaise, may be present. Dissemination of infection after 1 to 4 weeks results in metastatic abscesses, including lesions in visceral organs.

The interest in glanders as a biologic weapon stems from the fact that few organisms are required to cause disease; it is easily reproduced; high mortality is associated with inhalation; and there is a general lack of clinical recognition, which subsequently delays diagnosis and treatment. During World War I, horses scheduled for shipment to the Allies were deliberately exposed to B *mallei*. In a single year, the Soviet Union produced more than 2000 tons of dry glanders [11]. Glanders is an example of a disease that can have significant human health implications if used as a bioterrorism agent. Because this disease may not be easily recognized in people or animals, it is important for equine practitioners to be aware of this disease and to recognize that horses may serve as sentinels for a potential intentional biologic release.

Disease challenges that consume resources and energy

In the past two decades, the epidemiology of human rabies has changed. With the widespread use of rabies vaccine since the 1950s, human rabies cases have virtually disappeared. During the 1980s, most human rabies cases in the United States were attributed to exposure to wild dogs during foreign travel. These cases were infrequent. However, a disturbing trend appeared during the 1990s with an increase in human rabies cases attributed to bat exposures [12]. The reason for this re-emergence is not completely understood, except to highlight the adaptability of many of these emerging or re-emerging agents. Rabies is occasionally identified in horses; however, horses account for less than 1% of all rabid animals identified yearly. Since 1992, the number of reported equine cases ranges from 42 to 82. In the US literature, no documented human cases have been attributed to equine exposure, yet diligence is necessary because of the severity of human disease. Rabies in horses has a wide spectrum of clinical signs. Furthermore, there has been documented evidence of illness even in vaccinated horses [13]. Another interesting challenge, especially from rabid domestic animals, is the potential for large-scale human exposures. From 1990 through 1996, 22 large-scale episodes were reported in the United States [14]. Three of these episodes involved horses. Thirty-nine to 64 persons were potentially exposed to rabies in these three situations. This presents an economic and emotional challenge to identify potentially exposed cases and to ensure that they are receiving appropriate postexposure prophylaxis. Today, the current cost for post-exposure prophylaxis for an unvaccinated person is approximately US $2000. Unfortunately, these situations do occur in veterinary hospital settings. The frequency of these situations is unknown, but they typify the challenges that can occur from potential zoonotic threats in a hospital setting. It is important that we minimize the impact of these risks through appropriate infection control procedures, pre-exposure vaccination of all personnel who are in contact with patient animals, rapid notification of appropriate staff, and limiting contact with suspect animals. In the veterinary hospital setting, our goal should be to avoid these mass exposure situations and to develop plans that are implemented before these situations occur. This should limit hospital liability and protect employee and public health.

Diseases with an insidious and complex web of transmission

Salmonella infections and outbreaks in veterinary teaching hospitals are an ongoing challenge. The economic losses and potential human health infections are singularly forcing administrators at veterinary teaching hospitals to review, modify, and improve their infection control procedures. The challenges for clinicians in hospital settings include the proportion of subclinical cases that come into the hospital, the hospital design and layout, the development of antimicrobial-resistant strains, and the ability of some strains of *Salmonella* to persist in the hospital environment. The limited resources that are available to develop an adequate surveillance programs complicate this issue.

This was highlighted in an outbreak that occurred at the University of Minnesota, Veterinary Teaching Hospital (VTH). In August of 1995, an increase in *Salmonella* cases was observed among horses at the VTH. In addition, *Salmonella* spp were isolated from two students who were in contact with infected horses and subsequently developed diarrhea. Serotyping revealed that the isolates were *Salmonella* Typhimurium [15]. Because of the human illness associated with the equine cases and prior collaborations with the State Health Department, isolates were subtyped by pulsed-field gel electrophoresis (PFGE) and tested for antimicrobial susceptibility. The isolates from people and horses had similar multidrug resistance profiles, and the PFGE patterns were identical or clonally related.

The disturbing element of this outbreak was how long it persisted. The identical PFGE pattern was identified in horses and the environment for several months (Fig. 1). Often, *Salmonella* outbreaks are observed with a rapid succession of cases occurring over a short time. This was not the case in 1995 through 1996; sporadic cases were identified over a period of several months to a year. *Salmonella* persisted on environmental surfaces even after cleaning.

This pattern of disease transmission has been present in restaurant-associated outbreaks, with sporadic human cases detected over extended periods [16]. Furthermore, persistent environmental contamination was noted in some of these outbreaks. Another common feature among these restaurant-associated outbreaks was the associated employee illness. These types of outbreaks could be related to the low number of infectious organisms persisting in the environment, leading to low or moderate level transmission events over weeks to months. This may be the case in equine hospitals as well. Therefore, diligence is required to isolate and test diarrheic horses; limit personnel access; and train students, staff, and barn help to recognize and prevent continued transmission. Also, employee illness may serve as a point of recognition for potential outbreaks or nosocomial events. Employees with illness should promptly notify their hospital health officers or employers. Health officers should provide a mechanism by which employees can be evaluated by appropriate health care providers. These health care providers should be encouraged to submit appropriate diagnostic samples if a zoonotic illness is suspected. Furthermore, hospital administrators should work closely with occupational health providers to identify potentially infected employees and initiate a thorough surveillance program to identify suspect animal and human cases. Immunocompromised veterinary personnel, including those with malignancy, human immunodeficiency virus, or diabetes, and those receiving corticosteroid therapy or treatment with other immunotherapy agents are at particular risk. Mechanisms should be in place to reduce the risk of these employees being exposed to zoonotic pathogens. This may include temporary or permanent reassignment of duties, restriction of performing certain procedures or working with certain animals, and additional infection control education. These mechanisms should be dealt with prospectively so that employee (patient) confidentiality and occupation health and labor issues are appropriately addressed.

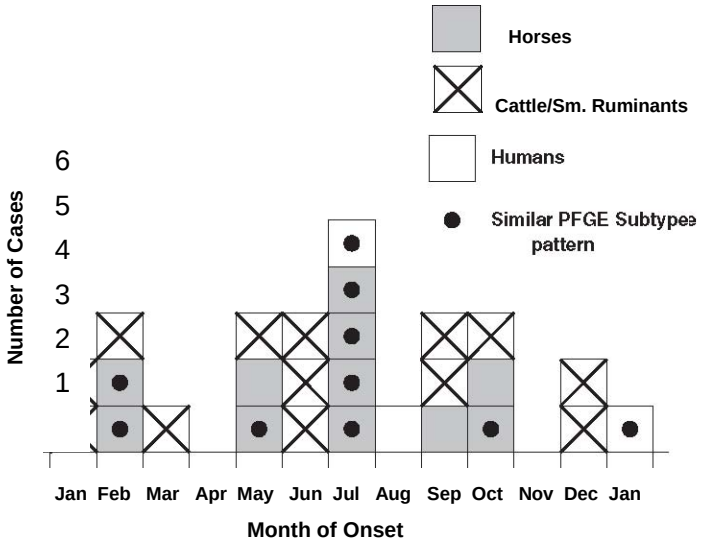

Fig. 1. Salmonella cases in the Veterinary Teaching Hospital, St. Paul, Minnesota, 1995.

Immunocompromised owner or employee

There is an increasing percentage of the human population that is immunocompromised. This is likely a result of the increased survival time of persons with cancer and other serious diseases, the increasing number of people with drug-or disease-induced immunocompromising conditions (particularly HIV infection), and an aging population. Previously, it has been demonstrated that the risk of zoonotic infections to immunocompromised people is low [17,18]. However, there is some concern about zoonotic disease acquisition when CD4 lymphocyte counts fall below 100 cells/mm^3. The most common zoonotic diseases of concern in immunocompromised people include cryptosporidiosis, salmonellosis, and toxoplasmosis (Table 2). Transmission of these diseases to the immunocompromised patient can occur from direct contact with animals, but they are more often transmitted from inadequately cooked foods (ie, *Toxoplasma gondii and Salmonella* spp) or contaminated water sources (*Cryptosporidium parvum*). Estimates of these zoonotic infections in HIV patients are variable. Fourteen percent of HIV patients with diarrhea had cryptosporidiosis [19], whereas 20% to 47% of Toxoplasma-seropositive HIV patients developed toxoplasmic encephalitis [20,21] and 10% of HIV patients developed salmonellosis [22].

The risk of opportunistic zoonotic infections from horses is likely low. The two most likely agents are *Salmonella and Rhodococcus equi*. Also, documented animal-to-human and human-to-animal transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) has occurred [23,24]. MRSA is a frequent cause of nosocomial infection in the human hospital setting. Recently, MRSA has also been identified among healthy people who have not been hospitalized and likely acquired their infection from community contacts (ie, community-associated MRSA). Whether animals serve as a source of human MRSA infections is yet to be seen.

Until recently, R *equi* has been considered strictly an equine pathogen. The incidence of R *equi* infection in people has increased markedly with the emergence of HIV. The first reported human R *equi* infection was in 1967 in a 29-year-old man with an autoimmune disease who worked at a stockyard [25]. Since then, more than 100 cases have been described in the literature, with most occurring in immunocompromised patients, especially HIV-infected individuals. This facultative, intracellular, gram-positive coccoba- cillus is likely acquired from inhalation of contaminated soil, from inoculation of a wound or mucous membrane, or via ingestion [25]. The main route of human infection is unclear, but some have postulated that contact with farm animals and manure may account for one third of cases [25,26]. Recently, virulence-associated antigens and plasmids have been identified. R *equi* virulence plasmid VapA commonly causes suppurative pneumonia in foals and is widespread on horse breeding farms [26]. However, only about 20% of R *equi* isolates from human infections express VapA. R *equi* virulence plasmid VapB has been found in the submaxillary lymph nodes of pigs, and some have postulated that pigs may serve as an important source for infections, especially in Southeast Asia [26].

Clinically, pulmonary involvement, including pneumonia, lung abscessation, and pulmonary nodules, is commonly described in human beings. Bacteremia is common in immunocompromised patients. A review of immunocompetent individuals with R *equi* infection identified 19 patients, 3 of whom had direct or indirect contact with horses or soil from horse farms [27]. R *equi* has been identified in other animals, including pigs, cattle, and goats. Instructions are given to immunocompromised patients, including transplant and HIV-infected patients, to avoid or limit contact with domestic animals. As greater proportions of our population are diagnosed with immunocompromising conditions, new challenges may present from organisms that are generally not considered zoonotic, such as R *equi*.

Table 2 Potential animal-associated infections among individuals with HIV infection

Agent	Frequency in HIV patients	Sources	Likely animal sources	Likelihood of infection from contact with horse
Toxoplasma gondii	Common	Undercooked meats, unwashed produce, soil while gardening	Cats	None
Cryptosporidium	Moderate	Water, people, direct animal contact	Farm animals	Rare
Cryptococcus	Moderate	Soil, bird droppings	Birds	None
Campylobacter neoformans	Moderate	Food of animal origin, contaminated vegetables, direct animal contact	Reptiles, farm animals, cats	Moderate
Salmonella	Low	Poultry, other meats of animal origin, raw milk, direct animal contact	Dogs, cats, farm animals	Rare
Bartonella henselae	Low	Cats		None
Giardia lamblia	Low	Person to person, water		None
Rhodococcus equi	Rare	Soil		Rare
Listeria monocytogenes	Rare	Soft cheeses, hot dogs, delicatessen meats, raw milk		Rare

Data from Angulo FJ, Glaser CA, Juranek DD, Lappin MR, Regnery RL. Caring for pets of immunocompromised persons. J Am Vet Med Assoc 1994;205:1711–8; and Glaser CA, Angulo FJ, Rooney JA. Animal-associated opportunistic infections among persons infected with the human immunodeficiency virus. Clin Infect Dis 1994;18:14–24.

Infection control in the human hospital setting

There are five main transmission routes for infectious agents. These are contact, droplet, airborne, common vehicle, and vector borne. Contact transmission can be direct, involving body-to-body contact, or indirect, in which a contaminated intermediate inanimate carrier passes an infectious agent from one host to another. Enteric infections, such as salmonellosis or cryptosporidiosis, can be spread by direct contact or via contaminated objects. Droplets are large particles generated by sneezing, coughing, or talking. They are propelled for a short distance from the source individual and cannot remain suspended in the air. Airborne transmission involves small particles (\5 lm) that can remain in the air for prolonged periods and travel over long distances. Common vehicle transmission occurs by contamination of food, water, or equipment, whereas animals like flies, fleas, mosquitoes, and ticks transmit vector-borne infections.

In the human hospital setting, precautions can be taken to prevent transmission of infection by the contact, droplet, and airborne routes [28]. In all cases, standard precautions include hand hygiene; wearing gloves when touching blood, body fluids, secretions, excretions, and contaminated objects; and wearing masks, eye protection, and gowns when there is a risk of soiling or splashing with blood or other body fluids. Contact precautions require isolation of the patient to a private room (or cohorting patients with similar infections) and extend standard precautions to include the use of gowns and gloves on entering the patient's room. Droplet precautions require placement of the patient in a private room and wearing a mask when working within 3 ft of the patient. With airborne precautions, the patient is placed in a room with negative air pressure (6–12 air exchanges per hour), appropriate ventilation, and the use of an N95 mask (or equivalent) by persons entering the room. These precautions may not always be practical or applicable in the veterinary setting, but many are needed to prevent nosocomial and potential human infections. The common prevention measures include the use of protective clothing and gloves to prevent direct transmission of pathogens, personal protective equipment for other agents transmitted by droplet or airborne routes, adequate hand hygiene, hospital-based standard operating procedures, and appropriate use of vaccines.

Summary

Infectious agents are insidious, often changing to adapt to host defenses or treatment advances. Because these challenges will continue, the need to apply standard and transmission-based precautions is important not only in the human hospital setting but in the veterinary clinic setting. In addition, to prevent human infection and potential liability, clinics need to establish program algorithms to prevent disease spread for specific agents or planned procedures to respond to potential nosocomial and zoonotic disease events. These need to be done proactively. Furthermore, more money needs to be dedicated to establish infection control programs and to improve the science of infection control in the veterinary setting.

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NOTES

MRSA - THE EMERGENCE OF A BAD BUG
INFECTION CONTROL AND PUBLIC HEALTH CHALLENGES

Jeffrey B. Bender, DVM, MS, DACVPM
University of Minnesota, Veterinary Public Health
136F ABLMS, 1354 Eckkles Ave
St. Paul, Minnesota
612-625-6203
bende002@umn.edu

INTRODUCTION:

S. aureus has long been recognized as an important human pathogen and is the leading cause of suppurative infections in humans, including superficial skin infections such as boils and furuncles as well as more serious infections such as bloodstream infections, pneumonia, osteomyelitis and endocarditis. *S. aureus* is also a major cause of nosocomial infections, including surgical site infections and infections associated with indwelling medical devices. Currently, the proportion of *S. aureus* isolates that are MRSA is more than 55 percent in some U.S. human hospitals. Established risk factors for MRSA include current or recent hospitalization or surgery, residence in a long-term care facility, dialysis, and indwelling percutaneous medical devices and catheters[1,2]. Recently, community-associated cases of MRSA have been recognized[3].

MRSA has recently been a concern in equine hospitals[4,5]. This includes wound infections and transmission between horses to humans and humans to horses[6]. As a result of these concerns, Veterinary Teaching Hospitals have developed surveillance and control programs, including periodic human surveillance, glove use when handling any horse and isolation of MRSA culture positive horses. MRSA has been reported in dogs [7-9] and rarely in cats. In 1988, an outbreak of MRSA was reported from a human hospital geriatric ward[10]. Thirty-eight percent of the nursing staff was positive for MRSA. It was assumed that the high rate of colonization was due to a ward cat. Infection control measures and removal of the cat led to resolution of the outbreak.

Recent MRSA infections in animals seen by clinical staff in the University of Minnesota, Veterinary Medical Center has created diagnostic and treatment challenges[11]. From October 2003 through December 2009, MRSA has been identified from 31 refractory cases presented to the veterinary medical clinic (Table 1). There has been a steady increase in the number of cases detected from 2003 through 2008. Ten (34%) of cases were identified in 2008 and two in 2009. Cases included 20 dogs, 7 cats, and 2 horses. Twenty-four isolates were sent to the Minnesota Department of Health for confirmation, antimicrobial susceptibility testing, and DNA fingerprinting. Seventeen of the 24 isolates have been characterized as clonal group USA100, representing strains commonly identified from recently hospitalized human patients (HA-MRSA). Other clonal groups include USA300, USA400, and USA500 representing community associated (CA-MRSA). With the identification of community associated strains, there is a detection of both USA100 and USA300 strains in human hospitals. This likely will be the case in veterinary hospitals. Veterinary isolates have all been multidrug resistant. Nosocomial spread is suspected from several case clusters (Shaded areas - see Table 1). This has been further supported with indistinguishable MRSA strains isolated from environmental surfaces and from clinicians.

Seventeen (71%) of 24 interviewed family members of the infected pet were recently hospitalized, diagnosed with MRSA, had on-going severe illnesses (i.e. chemotherapy), or were healthcare providers. No identifiable risk factors were reported in 6 instances and clustered temporally suggesting nosocomial events.

Pet owners were informed that a multidrug resistant organism was isolated from their pet. Client oriented fact sheets are presented to clients (http://www.cvm.umn.edu/cahfs/sheets/H-M/home.html). Clients were also contacted individually by a public health veterinarian to address potential concerns.

Table 1. MRSA clinical cases at the University of Minnesota, Veterinary Medical Center, 2003-2008

Date	Species	Source	PFGE subtype	Clonal Group
10/30/03	Feline	Abscess	MR11	USA100
12/4/04*	Feline	Skin	MR191	USA100
3/21/05*	Feline	Skin	MR191	USA100
6/8/05	Canine	Skin	MR191	USA100
6/8/05	Canine	Skin	MR360	USA100
7/27/05	Feline	Joint	MR4	USA100
10/13/05	Feline	Skin	MR391	USA300
2/21/06*	Canine	Skin	MR107	USA100
3/13/06*	Canine	Trachea	MR107	USA100
8/5/06	Canine	Chest tube	MR340	USA300
8/21/06	Canine	Pleural fluid	MR340	USA300
11/16/06	Canine	Wound	MR107	USA100
12/2/06	Canine	Skin	MR4	USA100
12/5/06	Canine	Bone	MR120	USA100
4/11/07	Canine	Skin	MR771	USA100
5/22/07	Canine	Wound	MR107	USA100
7/9/07	Canine	Wound	--	--
7/19/07	Equine	Abscess	MR882	USA500
8/14/07	Canine	Joint	MR391	USA100
1/4/08	Canine	Wound	MR391	USA100
1/7/08*	Canine	Incision site	MR307	USA300
1/11/08*	Canine	Wound	MR307	USA300
2/22/08	Feline	Urine	--	--
3/18/08	Canine	Skin	--	--
6/17/08	Canine	Incision site	--	--
6/26/08	Canine	Incision site	MR340	USA300
8/21/08	Canine	Urine	--	--
8/30/08	Equine	Incision site	MR959	USA400
9/19/08	Feline	Urine	MR958	USA100
4/20/09	Feline	Urine	--	--
7/28/09	Canine	Wound	--	--

*temporal clusters of indistinguishable subtypes

MRSA and Horses

There appears to be geographic differences in equine prevalence of MRSA. Increasing prevalence has been reported in the Netherlands, while in Eastern Canada no MRSA cases were identified in 497 horses sampled[12,13]. In addition, a recent study has demonstrated that colonization of MRSA was 10% in veterinary personnel attending an equine veterinary conference, which is higher than the colonization prevalence in the general public[14]. In a recent multi-center study in North America, both CA-MRSA and HA-MRSA were identified in horses[15]. HA-MRSA was more commonly isolated from horses with infected incisions.

Community Studies – Human/Animal Interface

To characterize the potential for interspecies transmission of MRSA, several community studies were conducted. This included the collection of nasal and rectal swabs from asymptomatic animals in a long-term care facility and pets of human patients recently diagnosed with MRSA. Two of 11 resident cats from the long-term care facility were identified with MRSA. Isolates were genotype USA100 (HA-MRSA). MRSA was isolated from 2 of 28 asymptomatic pets of pet owners previously diagnosed with

community-associated MRSA. Isolates from the 2 animals were genotype USA300 (CA-MRSA). These studies demonstrate the potential for interspecies transmission in community settings and in a long-term care facility. Colonized animals in these studies were asymptomatic and appeared to be transiently colonized[16, 17].

Infection Control Strategies

The single most important prevention measure is appropriate hand hygiene. Personnel should wash their hands between handling each animal. This will decrease the risk of pathogen transmission to other animals and to staff. It is also important to incorporate "standard precautions" to protect staff and prevent movement of MRSA. This may include appropriate isolation and disinfection protocols. Staff should be aware of the potential risks and notify appropriate clinic personnel to prevent nosocomial and zoonotic spread. Immune deficiencies may put personnel at an increased risk. Individuals with an immune dysfunction should discuss their status with their employer, so that appropriate preventative measures can be taken. Ideally, veterinary clinics should provide "right to know" materials and have in place procedures to reduce zoonotic disease transmission.

SUMMARY

Pets with MRSA likely acquire their infection from their owners as demonstrated by the presence of common genotypes among the various populations. Horses similarly can acquire MRSA from their human care-takers, the hospital, or other horses. There is a need to re-enforce precautionary measures and hand hygiene to pet and equine owners diagnosed with MRSA infection. Owner education should describe the potential risk of transmission from and/or to companion animals. Further research to quantify this household risk, the length of carriage, and the potential treatment options is needed. In addition, stringent precautions are necessary to prevent environmental contamination and spread by staff within veterinary clinics.

The emergence of MRSA in companion animals highlights the importance of astute clinical and microbiologic monitoring for multi-drug resistant infections. In addition, there is a need to train veterinary practitioners and students about these new pathogens and their potential for nosocomial spread. The development of integrated human/animal surveillance systems and continued communication between human and veterinary professionals can help to identify new infections and treat those infections crossing species.

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Key Words: MRSA, zoonoses, antimicrobial resistance, methicillin-resistance *Staphylococcus,* Companion animals

NOTES

UNDERSTANDING SHAMPOO THERAPY

White, PD
Atlanta Veterinary Skin & Allergy Clinic, PC
2803 Shallowford Road, Atlanta, GA 30341

INTRODUCTION

The skin is a formidable force providing physical, biochemical, microbial and immunologic protection. There are many players in the microenvironment of the skin (microbes, enzymes, lipids, proteins, immune products) that are key in keeping the skin healthy. An upset in any one of these could help create a disease state. Luckily "Mother Nature knows best" and it is only in extreme or chronic disease states that the skin needs help in correcting this imbalance. Shampoos and rinses are one therapeutic modality that can help.

It is important to state at the outset that *shampoo therapy* in veterinary medicine is *skin* therapy rather than hair therapy. Product selection is determined by the current condition of the skin along with a desire to change this for the better. To optimize this form of therapy two things must be in place. One is an understanding of "normal" physiologic processes of the skin, from epithelialization and cornification to the actions of the epidermal barrier. The other is an understanding of the components in the product we choose and how it works to correct the disordered skin condition.

To arm oneself with the knowledge and understanding of how the skin functions in health and disease provides a set of tools needed to recognize where the problem probably has occurred, then select therapy that targets the part of the process that is broken.

EPITHELIALIZATION AND BARRIER FORMATION

The microenvironment of the skin is quite complex with a primary function to protect. Keratinocytes originate in the basal cell layer. Epidermal stem cells give rise to daughter cells that, through several cycles of mitosis, begin the process of epithelialization (spinous layer). As these cells migrate upward they begin to loose their proliferative abilities in favor of synthesizing specific proteins (pro-fillagrin, loricrin and involucrin) and lipids (polar lipids, glycosphingolipids, free sterols, phospholipids and catabolic enzymes). Further differentiation sees the beginning of the organization of the synthesized proteins into bundles (keratohyalin granules) and the lipids into micro - vesicles called lamellae (granular layer). These lipids are enzymatically converted to cholesterol, fatty acids and ceramides as the lamellae make their way to the surface of the cell. It is in this layer of the epidermis that both the cell envelope and the intercellular "cement" begin to form. The lamellar membrane fuses with the cell membrane emptying the lipid contents into the intercellular space forming the intercellular lipid domain. Enzymes present in these cells begin to modify the precursor proteins and link them to the desmosomal structures of the cell ultimately forming the cornified envelope of the stratum corneum (SC). This progressive and programmed cell death is the terminal stage of differentiation. Desquamation occurs with the hydrolysis of cholesterol sulfate and the breakdown of desmosomes. A disruption in any of these steps results in an abnormal barrier.

From a simplistic standpoint, the epidermis with the stratum corneum (bricks-corneocytes), the intercellular cement (mortar), and the surface interface made of glandular secretions, microbes, and immunologic products create the most important part of the barrier. The nucleated epidermis contributes to this barrier through tight, gap and adherens junctions, as well as through desmosomes and cytoskeletal elements. But it is the permeability barrier made up of the stratum corneum and intercellular lipid domain that is the most important part of this defense. The stratum corneum provides mechanical protection as well as a barrier to both water loss and permeation of soluble substances from the environment into the body. Together these structures create a semi-permeable water repellant and water retaining barrier that both repels harmful things and prevents internal dehydration. Regulation of permeability, desquamation, antimicrobial killing, and toxin and chemical exclusion is the responsibility of the intercellular product. The skin's immunologic capabilities are derived from the presence of langerhans cells, keratinocytes, and epidermotrophic T lymphocytes. Keratinocytes specifically can be activated to produce and express cytokines in response to injury and disease.

WHEN THINGS GO WRONG

When injury occurs, the skin's response is to thicken and exfoliate – a shift toward proliferation. Fortunately the skin's ongoing process of growth and differentiations provides a means for this organ to continuously renew and repair itself. Once corrected, the skin will go back to its normal, programmed process of growth, differentiation and exfoliation. Diseases where there is a significant disruption in barrier function are inflammatory diseases such as infections, irritant or contact allergies, atopic dermatitis, and seborrheic disorders. Shampoo therapy is key in the management of these diseases. The vast numbers and varieties of new shampoos and rinses provide an opportunity to develop very specific topical therapy for each patient. However, these choices also can be confusing and the wrong choice may retard resolution of or even aggravate the condition.

Contact irritant and hypersensitivity reactions result from direct contact with irritants or allergens. Shampoos and rinses mechanically remove these substances. Atopic dermatitis (AD) in humans and dogs is a complex disease syndrome where pruritus, recurrent pyoderma, recurrent malassezia dermatitis, and various alterations in the normal cutaneous microenvironment occur. The traditional "inside-outside theory" of AD in humans and dogs postulates that a genetic defect causes an abnormal immune system, which leads to the inflammation and symptoms of AD. A newer "outside-inside theory" states that there is a genetic defect in the normal skin barrier of the skin which leads to a higher exposure to environmental allergens and the increased potential for development of sensitization. Further exposure leads to activation of keratinocytes which leads to inflammation and the subsequent signs of AD. There is altered lipid and ceramide composition of the stratum corneum, dysfunctional TEWL, and increased keratinocyte activation in AD. Keratinocytes are activated more readily in AD than in normal individuals and this activation results in increased inflammation. Activated keratinocytes usually release defensins (antimicrobial peptides) that help protect against the development of infection, but fewer defensins are released in AD leading to a higher number of skin infections. Exotoxins released by staphylococcal bacteria can activate and perpetuate the allergic response. Although not yet proven, it makes sense that this process may also take place in dogs because of the frequent occurrence of Staphylococcal and malassezia infections with canine atopic dermatitis (CAD). CAD may begin as a problem in barrier function; this increases exposure to environmental allergens with stimulation of the cutaneous immune response. Cutaneous infections (pyodermas, malassezia dermatoses, dermatophytosis) are almost always accompanied by inflammation, crusts, scale and erosions as a result of self trauma, a disrupted stratum corneum and disordered epidermal differentiation. Systemic and topical medications work synergistically to rid the skin of the offending pathogen and to re-establish the normal microenvironment.

WHY SHAMPOO THERAPY IS KEY

Shampoo therapy has long been the mainstay of managing dermatologic disorders in veterinary medicine. Easy access to skin allows both frequent application and frequent assessment of response. Duration, type and interval of treatment can be adjusted based on the individual's response. The process mechanically removes dirt, keratinaceous debris and allergens from the skin. It is cooling and rehydrating. A predictable benefit of this process is reduced exposure to allergens and other pruritogenic factors and at least temporary relief. Water rehydrates the stratum corneum but the benefit is only temporary unless a moisturizer is used to trap the water in the SC. So the best use of a moisturizer is after a cleansing shampoo to trap water in the SC and prolong rehydration. In addition to cleansing, shampoos provide a vehicle for applying a variety of medications. The active ingredients penetrate the skin through intercellular spaces (lipophilic molecules), through keratinocytes (negatively charged), and through the hair follicles. Newer technologies (liposomes, novasomes, spherulites, micelles, etc) allow these active ingredients to stay in contact with the skin longer resulting in prolonged effect. Shampoo therapy is rarely the sole form of treatment but can be invaluable in reducing the time to clinical resolution while providing a window of increased comfort for the pet until a definitive diagnosis and more specific treatment options can be identified.

If the barrier is abnormal in dogs with atopic dermatitis, shampoo therapy has the ability to normalize this process while depopulating the bacteria and yeast, and removing allergens from the skin. In fact in any condition where barrier dysfunction has developed over time (infections, keratinization disorders, hypothyroidism, exfoliative dermatitis) shampoo therapy is a helpful adjunct to therapy. In normal skin, several processes, such as desquamation, normal keratinocyte activation with the production of cytokines, chemicals in glandular secretions, normal microflora, intercellular and cell surface lipids and sugars all help

control bacterial overgrowth. Therefore infection can not occur unless the homeostatic processes are somehow disrupted. Secondary yeast and bacterial skin infections are the conditions that are common to most dermatologic problems. Skin infections start with the adherence of the microorganism to cell surface sugars (glycoproteins) via surface proteins called lectins. Once attached, they have ability to overgrow and spread. Attached bacteria also activate keratinocytes to produce cytokines which in turn cause inflammation.

THE BASICS

Hydrotherapy (just water) has the benefit of mechanically removing dirt, crusts, dead skin cells, allergens, as well as being cooling and rehydrating. A cleansing shampoo with sufficient surfactants to break up and remove accumulated debris is done first to prepare the skin to receive the maximum benefit from the selected medicated shampoo. A medicated shampoo is chosen based on the condition needing attention. It must be massaged into the skin for 10-15 minutes to allow the active ingredient(s) to penetrate and have its effect, and then rinsed thoroughly. Clipping the fur short may be needed to facilitate this process. Shampoo, when lathered with water, cleans the fur and skin but will also remove the natural oils (sebum) resulting in a dry skin condition. Emollients (seal moisture at the skin surface) and humectants (draw moisture from the dermis into the skin) prolong the rehydrating benefits of hydrotherapy by trapping the water close to and in the skin, and are often applied after the medicated shampoo to help prevent dryness.

Shampoo selection is based on identifying the specific problem at hand and choosing an active ingredient (s) that will help correct the problem (see table). **Keratomodulating products** work to restore normal keratinocyte growth and differentiation by working on the basal cell layer and reducing the rate of division. Products that work in this way are called keratoplastic. Keratolytic products may remove excess scaling by increasing desquamation and/or reducing intercellular cohesion. Many products are both keratolytic and keratoplastic and include salicylic acid, sulfur, selenium sulfide, benzoyl peroxide and tar. Tar and selenium sulfide should never be used on cats.

Antiseborrheic products theoretically reduce sebum production and help remove stagnant oil and debris from the sebaceous gland ducts. Certainly, products in this category are degreasing and can be drying if an effort is not made to re-establish a moist, healthy environment after stripping away the debris. Antiseborrheic products include benzoyl peroxide, sulfur, tar and selenium sulfide. **Antibacterial products** include chlorhexidine, povidone iodine, benzoyl peroxide, acetic acid and ethyl lactate. **Antifungal products** include the keratomodulating products in addition to products with direct antifungal properties (miconazole, chlorhexidene, ketoconazole). **Anti-pruritic** therapy is multifactoral. Anything that reverses dryness, removes allergens and surface debris, and prolongs rehydration of the SC has the potential to be antipruritic. Products that restore barrier function, kill bacteria and malassezia, and reduce inflammation are also antipruritic. Ingredients with specific antipruritic activity have also been added to shampoos, sprays and rinses and include colloidal oatmeal, pramoxine (a topical anesthetic), diphenhydramine (an antihistamine), hydrocortisone and triamcinolone (glucocorticoids).

NEW TECHNOLOGY - WHAT MAKES GOOD THINGS WORK BETTER

Most skin abnormalities have a dry component. Moisturizing factors are often either added to the shampoo or placed in an after-shampoo spray or rinse to help reverse the dryness that can occur as a result of stripping the normal moisturizers from the skin with the medicated shampoo, or to help re-establish the normal skin environment. The term moisturizer implies that the substance applied adds or retains water in the skin. This may be done by providing natural exogenous humectants (urea, propylene glycol, glycerin, lactic acid) or an exogenous barrier to water loss (petrolatum or natural or synthetic oils). Other moisturizing factors include emollients, humectants, occlusives (heavier seal than emollients), fatty acids (incorporated into intercellular space to help maintain the epidermal barrier), and emulsifiers (help distribute oil or humectant evenly over the skin).

Cell membranes are made up of phospholipid bilayers. In the presence of water, the heads are attracted to water and line up to form a surface facing the water. The tails are repelled by water, and line up to form a surface away from the water. In a cell, one layer of heads faces outside of the cell, attracted to the water in the environment. Another layer of heads faces inside the cell, attracted by the water inside the cell. The hydrocarbon tails of one layer face the hydrocarbon tails of the other layer, and the combined structure forms a bilayer.

The newer technologies of micro-encapsulation enhance the re-hydrating effects of moisturizing products and increase the availability of active ingredients to the target site. They do this by mimicking cell membranes. Microvesicle technology is a method used to package and deliver active ingredients onto skin. Micelles are very small unilamellar, spherical structures made up of bipolar lipid molecules that have hydrophilic (head) and a hydrophobic (lipophilic) ends. These microvesicles can be charged or neutral. The positively charged (cationic) microvesicles bind to negatively charged skin allowing prolonged contact of the active ingredient with the surface of the skin and hair. On contact with the skin the chemical bonds in the micelle break down delivering the content of the micelle to the skin. At the same time it delivers the active ingredient to the skin it attracts and traps dirt and debris. This trapped debris is rinsed away at the end of the shampoo. Neutral micelles pass through the surface barrier and are deposited in the deeper layers of the skin where they have the desired effect.

Spherulites® and Novasomes® are multi-lamellar with either a positive or neutral charge depending on the desired effect. Each layer of the capsule is a diffusion barrier to help control the release of the active ingredient from the central core. The hydrophilic portion tends to hold the active ingredient in the capsule until it comes in contact with the skin. Then the lipophilic end ensures prolonged contact with skin.

Spherulites® are multi-layered microvesicles made of surfactants. Positively charged spherulites adhere to negatively charged skin and are active on the surface. The non-ionic spherulites are not charged and are capable of penetrating into the skin. Each layer has both a lipophylic and a hydrophilic portion which allows the incorporation of both hydrophilic and lipophilic ingredients. As each layer gradually breaks down the active ingredients are released onto the skin, enhancing contact time and providing a sustained effect of the active ingredient. Cutaneous bio-mimetic ingredients such as ceramides, essential fatty acids, and cholesterol are added to the microvesicle to help re-establish hydration and epidermal integrity. Chitosanide coats skin and fur and traps the spherulite next to skin to extend the activity of the active product increasing moisturizing effect. Spherulites® are used in Virbac products.

Novasomes® are composed of synthetic multilamellar amphiphilic molecules surrounding a large amorphous core. Novasome® vesicles have up to seven lipid bilayer membranes surrounding the central cargo hold which may contain an aqueous, lipid or solid product. 80% of the central area contains water and lipids. Positively charged particles adhere to the negatively charged skin and slowly release the central area products as the layers break down. Novasomes are used by Vetoquinol in several of their shampoos and rinses.

While microvesicle technology helps deliver products to the skin, anti-adhesive technology has been utilized in shampoo therapy to help treat skin infections. Research has shown that four sugars, D-mannose, D-galactose, L-rhamnose and alkylpolyglucoside, mimic the sugar moiety in cutaneous glycoproteins. These can bind both the cutaneous sugars and microbial lectins, and thus keep microbes from binding to the skin. This anti-adhesive technology is called **Glycotechnology**. Studies have shown that these sugars bind lectins on the surface of Staphylococcus *intermedius, Pseudomonas auregenosa,* and *Malassezia* thus preventing them from adhering to the skin surface. In addition, Glycotechnology reduces keratinocyte activation and cytokine signaling thereby reducing inflammation. Glycotechnology is used in Virbac's line of shampoos, ear cleaners and leave on conditioners.

Dry skin and other skin disorders are characterized by impaired stratum corneum (SC) barrier function and by an increase in transepidermal water loss (TEWL) leading to a decrease in skin hydration. It has been demonstrated that products containing SC lipids could play a part in the restoration of disturbed skin barrier function. **Phytosphingosine** is a lipid that occurs naturally in the stratum corneum, both in its free form and as part of ceramides. It has both anti-inflammatory and anti microbial activities. It has also been synthesized and incorporated into shampoo as a means of barrier repair. Phytosphingosine and micelle technology are use in the Sogeval line of products.

Lysozyme, Lactoperoxidase, and Lactoferrin are 3 enzymes derived from milk products. Each enzyme has its own unique antimicrobial properties. Lactoperoxidase, which when combined together with hydrogen peroxide, thiocyanate and/or iodide, produce a potent antibacterial system known as the Lactoperoxidase System. Two hypohalous ions, hypothiocyanate or hypoiodite, are both bactericidal and fungicidal. Lysozyme kills bacteria by disrupting the formation of a glycosidic bond between the two components of peptidoglycan in bacterial cell walls. Lactoferrin is an iron binding protein. It is bacteristatic against a wide range of microorganisms including gram-negative and gram-positive bacteria and may inhibit the growth of bacteria by depriving them of iron. This enzyme system is incorporated in the Zymox brand of topical products.

SUMMARY

Topical therapy, especially shampoos, helps augment barrier function (both antimicrobial and permeability) and re-establish a normal microenvironment. Every patient is different so it is important to identify the primary disease and consider all factors that may contribute to the skin condition before choosing a shampoo product. Always treat secondary infections specifically with both topical and systemic medications in every case. Remember, the best success is appreciated with a thorough understanding of the active ingredients in shampoo products. Get to know your chosen product – before you choose to use it!

Pet King Brands (pkb) AH, Inc – milk enzyme technology - Zymox products
Sogeval Laboratories - Phytosphingosine technology - Duoxo products
Vetoquinol USA. Novasome technology, EVSCO products
Virbac Animal Health US. Spherulites technology and Glycotechnology – Virbac products

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NOTES

ALL THOSE SHAMPOOS – HOW TO CHOOSE?

White, P
Atlanta Veterinary Skin & Allergy Clinic, PC
2803 Shallowford Road, Atlanta, GA 30341

We all know that the skin is the largest organ of the body and functions to provide both physical and immunologic protection as well as a way to maintain hydration and temperature control. Shampoo therapy is one way we can maintain a healthy skin and coat, or re-establish health in disease. In addition to understanding normal epidermal structure and function, there are four principles that are important to follow to maximize the potential benefits of shampoo therapy. First, make a diagnosis. Shampoo selection may well be different if you are treating an oily seborrheic dermatitis caused by a chronic Malassezia infection due to allergy versus a chronic keratinization disorder caused by a genetic condition. Second, know what ingredients are in the shampoo you choose and how each one works. Third, understand your client's needs and the pet's disposition. And lastly, re-evaluate and adjust therapy as needed. Now that we know what is in shampoos and how they work, let's see if we can apply these principles to real life cases.

SHAMPOO THERAPY FOR INFECTIONS

Antibacterial and antifungal shampoos are rarely effective alone in resolving infections unless the condition is mild, but they are invaluable as adjunct therapy. Antimicrobial shampoos are used to treat both superficial and deep infections, remove exudates, and help prevent infections in animals that are prone to reoccurrence. These shampoo ingredients reduce the surface colonization of the skin and fur. There are a variety of ingredients in medicated shampoos that are directed at killing microorganisms on skin. Chlorhexidene (.5-4%), triclosan, ethyl lactate (enzymatically changed to ethanol (lipid solubilizer) and lactic acid (lowers pH by bacterial lipases in hair follicles and sebaceous glands), and benzoyl peroxide (BP-2-3%) all have antibacterial effects. Benzoyl peroxide has the highest antibacterial activity as it oxidizes to BP free radicals which then disrupt bacterial cell walls. Phytosphingosine is both antibacterial and antiseborrheic. Chlorhexidene, ketoconazole (2%), miconazole (2%), benzoyl peroxide and acetic acid are all effective in killing fungus. Several ingredients are often combined in the same product to enhance the efficacy of the shampoo. When frequent shampoos are needed, microvesicle technology may help prolong rehydration and prevent dryness.

Case 1

Shampoo therapy for keratoseborrheic conditions

Crusting and scaling disorders, whether dry, waxy or oily, can be normalized in part by antiseborrheic shampoos. Seborrheic dermatitis is most often secondary to a primary disease so treating it often resolves the seborrheic condition. Active ingredients in this category increase desquamation by softening corneocytes and reducing intercellular cohesion (keratolytic), are cytostatic to the basal cell layer (keratoplastic), and may have antimicrobial and antipruritic benefits as well. Common ingredients include sulfur, salicylic acid, coal tar, selenium disulfide, and benzoyl peroxide.

Sulfur is mildly keratolytic (increases desquamation), keratoplastic (by a reaction with cysteine in the skin to form cystine and hydrogen sulfide, which are the building blocks for normal keratinization; or by dysregulation of normal maturation of keratinocytes by suppressing epidermal growth). It is also antimicrobial due to hydrogen sulfide and pentathionic acid that forms. It is also antiparasitic and antipruritic. It is typically present in equal concentrations with salicylic acid as the two are synergistic. Its side effects include its odor and staining potential as well as its drying effects. Salicylic acid is keratolytic (by disrupting intercellular cement), keratoplastic, antipruritic, and decreases the pH of skin resulting in increased hydration of the stratum corneum. Tar is another antiseborrheic ingredient and comes in a variety of forms (coal tar, solubilized tar, coal tar solution). It is often included with sulfur and salicylic acid. It is keratoplastic (antimitotic on the basal cell layer), antipruritic, vasoconstrictive, and degreasing. Benzoyl peroxide is quite versatile in that it is not only antiseborrheic and keratolytic, but it is antimicrobial and is reported to have follicular flushing effects as well. Side effects include dryness, irritation, and increased pruritus. Zinc gluconate down regulates sebum production.

Case 2

SHAMPOO THERAPY FOR PRURITUS AND ALLERGIES

Antipruritic shampoos are typically mild and classified as hypoallergenic. In addition to reducing pruritus they are designed to rehydrate dry skin and may fall into the category of moisturizers, humectants, and/or essential fatty acids. Shampoos and rinses in this category may contain non-lipid emollients (urea, lactic acid, glycerin, and propylene glycol), colloidal oatmeal, hydrocortisone (1%), diphenhydramine, pramoxine (1%), linoleic acid, gamma linolenic acid, mono and oligosaccharides, and vitamin E.

Case 3

SUMMARY

The first question to ask yourself is "What am I treating?" Stratum corneum retention (hyperkeratosis, scaling) or epidermal thickening (lichenification with crusting) indicates the use of a keratolytic or keratoplastic product. An oily or greasy condition warrants the use of an antiseborrheic product, while the presence of an infection demands the use of antimicrobials. Always treat secondary malassezia or staph bacterial infections specifically. Select the strongest shampoo appropriate for the clinical condition and use it up to 2-3 times weekly initially, and use a moisturizing shampoo or follow with an oil or humectant rinse to prevent excessive dryness. Re-evaluate every 3-4 weeks and adjust shampoo type and the frequency of treatments if appropriate. But first and foremost, don't forget to identify and treat the primary disease.

COMPARISON OF SHAMPOO INGREDIENTS BY ACTION AND CONDITION

P.White-NAVDF2010

	Ingredient	Action	Normal	Itchy	Dry	Oily	Dryw flaking	Oilyw/ flaking	Folliculitis	Pyoderma	Malassezia	Dermatophytes
	Benzoyl peroxide	antimicrobial, keratolytic, antiseborrheic, follicular flushing				X		X	X	X	X	
	Sulfur	keratolytic, keratoplastic, antimicrobial anti-parasitic, antipruritic, antiseborrheic		X		X	X	X		X	X	X
	Salicylic acid	Solubolizes intercellular cement; keratolytic, antimicrobial; decreases pH allowing better hydration			X	X	X	X		X	X	X
	Tar	keratolytic, keratoplastic, antimicrobial degreasing				X		X		X	X	
	Selenium sulfide	keratoplastic,keratolytic,degreasing, antifungal				X		X		X	X	X
	Chlorhexidene	antibacteral, antifungal			X	X	X	X	X	X	X	
	Ketoconazole	antifungal									X	X
	Miconazole nitrate	antifungal									X	X
	Triclosan	Mildly bacteriostatic								X		
	Pramoxine	anesthetic, anti-itch	X	X	X		X			X	X	
	Colloidal oatmeal	soothing, antipruritic, bindswater; rehydrating	X	X	X		X					
	Aloevera	soothing,antipruritic	X	X								
	Acetic acid	acidifying, rehydrating, antimicrobial	X	X	X		X			X	X	X
	Hydrocortisone HCl	anti-inflammatory, anti-pruritic		X								
	Zincgluconate	antibacterial, antiseborrheic			X	X	X	X		X		
	Ethyllactate	antiseptic, keratoplastic								X	X	
	Boric acid	acidifying, rehydrating	X	X	X		X					
	Menthol	cooling, antipruritic	X	X	X	X	X	X	X	X	X	X
Moisturizing Agents		Rehydrate and restore superficial skin film	X	X	X	X	X	X	X	X	X	X
Lipd emollients			X	X	X		X		X	X	X	X
	EFAs (linoleicacid, gamma)	Lipidemollients are greasy										
	linolenicacid)	Hydrates epidermis										
	Mineral oil, petrolatum											

Non-lipid emollient/moisturizer			x	X	X	X	X	X	X	X	X	X
	Urea	proteolytic, antibacterial, promotes hydration										
	Glycerin	Miscible in water and alcohol; attracts water										
	Propylene glycol	Miscible in water andd issolves oils										
	Lacticacid (citrus fruit acid)	Balances pH										
	Lanolin											
EnhancingTechnologies												
	Phytosphingosine	pro-ceramide; antiseborrheic, antimicrobial		X	X		X	X	X	X		
	Novasome microvesicle	humectant	x	X	X	X	X	X	X	X	X	X
	Glycotechnology	Antibacterial, antipruritic		X			X	X	X	X	X	
	Spherulites	humectant	x	X	X	X	X	X	X	X	X	X
	Mono and oligosaccharides	antibacterial, antimalassezial			X	X	X	X	X	X	X	
	Milkenzymes	antibacterial, antimalassezial	x		X	X	X	X	X	X	X	

NOTES

MALASSEZIA-OPINIONS ON MANAGEMENT

Mason KV[1], Morris DO[2], Ghubash R[3]
[1]Animal Allergy and Dermatology Service, Queensland, Australia
[2]Matthew J. Ryan Veterinary Hospital, University of Pennsylvania, Philadelphia, PA, USA
[3] Animal Dermatology Clinic, Marina del Rey, CA, USA

INTRODUCTION

The yeasts of the Malassezia [Pityrosporum] genus are in the family Cryptococcaceae and class Basidiomycetes. The non-lipid dependant *Malassezia pachydermatis* is found on dogs and cats, and the lipid dependant *Malassezia sympodialis* is found on cats and man.

Malassezia species have a characteristic peanut shape and monopolar budding with a collar that forms at the site of budding. These lipophilic yeasts are virtually confined to the skin of warm-blooded animals, but their distribution in nature has not been fully explored. Important to their cutaneous habitat are lipids, with most species being lipid-dependant for growth. Only one species, *Malassezia pachydermatis*, will grow without lipids; however, its growth is substantially enhanced in the presence of lipids. In dogs and cats, *Malassezia pachydermatis* colonizes the skin during the immediate perinatal period, and is the primary yeast species associated with skin and ear canal disease. On healthy dogs and cats, Malassezia are part of the normal cutaneous flora, with the principal carriage sites being the mucocutaneous areas, ears and interdigital regions. Cutaneous and immunological factors can cause this yeast to multiple and aid in it becoming a pathogenic organism, resulting in infections on and in the stratum corneum.

PATHOGENESIS

The pathogenesis of Malassezia dermatitis is multi-factorial and varies depending on underlying disease. Malassezia yeast colonize the skin and external ear canals of animals in very low numbers; however, in a diseased state, alterations in the skin's surface microclimate contribute to increased susceptibility to yeast infection. Primary diseases that cause increased moisture and humidity, alter surface lipids, increase staphylococcus numbers and/or disrupt the stratum corneum barrier function encourage secondary overgrowth of the yeast organism. These include pruritic inflammatory diseases (allergic and parasitic), endocrinopathies, and metabolic diseases, such as zinc-responsive dermatosis, superficial necrolytic dermatitis of dogs, and thymoma-associated dermatosis of cats.

CLINICAL PRESENTATION IN DOGS

Malassezia dermatitis typically causes pruritus with the primary lesion of erythema, but secondary lesions are very common and include excoriations, seborrheic plaques, hyperpigmentation, lichenification, crusts, scale, maceration and intertrigo. Yeast dermatitis closely resembles staphylococcal pyoderma, and cytology needs to be done to differentiate between them or determine if they are both present. Some dogs with Malassezia are more dry and flaky (seborrhea sicca), whereas others are more tacky/greasy (seborrhea oleosa). The distribution pattern is variable and can be generalized, although commonly affected areas include the periocular and perioral skin, interdigital spaces and claw folds, intertriginous areas (axilla, groin, body folds), ventral aspect of the neck, and flexure surfaces of the limbs.

Malassezia yeast also play an important role in cases of ceruminous otitis externa, in which they are highly pro-inflammatory. Some cases appear to be primary and associated only with moisture trapping, especially in swimming dogs. Malassezia otitis can be painful, pruritic, and erythematous and can present with either a yellow greasy exudate, or a dry brown/black wax.

CLINICAL PRESENTATION IN CATS

Malassezia dermatitis is unusual in the cat, in contrast to its common occurrence in the dog, and causes variable pruritus. It has been reported in pruritic/inflammatory dermatoses such as atopic dermatitis, adverse food reaction, and ectoparasitism. However, it has also been reported to occur often in cats with paraneoplastic skin diseases, such as paraneoplastic alopecia (secondary to pancreatic or hepatobiliary carcinoma) and thymoma associated dermatoses. Malassezia otitis in the cat is not uncommon, and is often pruritic.

DIAGNOSING MALASSEZIA DERMATITIS AND OTITIS

In the canine, the presence of ≥1 yeast/high power field (HPF) (400X) on the skin and ≥5 yeast/HPF in the ears are generally considered abnormal. However, canines may mount a hypersensitivity response to *Malassezia pachydermatis* even in extremely low numbers, resulting in a pathological effect despite the presence of a "normal" amount of yeast organisms. Therefore these definitions of normal and abnormal are only a guideline.

Cytology will reveal oval or elongated cells of 3-5 µm in diameter with a typical single polar budding (footprints, peanuts, etc). Adhesive tape stripping, skin scrapings on dry skin and direct impression smears with glass slides on greasy skin are all effective cytologic collection methods for the skin. Obtaining exudate with cotton tipped swabs and rolling the exudate on glass slides is the preferred collection method for otitis. A cotton tipped swab or metal spatula can be used to scrape the claw fold and roll the resulting exudate on a glass slide when evaluating for Malassezia paronychia.

Malassezia organisms can be demonstrated on histopathology, but the sensitivity is less than that of cytology. If the organisms are not present on a biopsy sample, that does not eliminate the possibility of them being present on the patient.

MALASSEZIA HYPERSENSITIVITY AND THE USE OF IMMUNOTHERAPY

In some dogs with atopic dermatitis (AD), antigens produced by *M. pachydermatis* may be recognized by the immune system as allergens [ie., Malassezia hypersensitivity (MH)], in which case a highly inflammatory and pruritic response can be mounted to relatively low numbers of yeast organisms, blurring the line between cytological definitions of "colonization" and "infection". However, many dogs with MH will also have overt infection, as defined cytologically by overgrowth of yeast on the skin surface. Malassezia hypersensitivity has not yet been studied or defined in cats with allergic skin disease, although Malassezia overgrowth does appear to contribute to the pruritic threshold of some cats with AD.

Evidence to support the role of *M. pachydermatis* as an allergen in canine AD includes increased intradermal test (IDT) reactivity to crude extracts of *M. pachydermatis*,[1,2] increased serum concentrations of anti-Malassezia IgE as determined by the use of enzyme-linked immunosorbent assay (ELISA),[3] and the successful passive transfer of cutaneous anaphylaxis via atopic canine serum (which harbored high titers of anti-Malassezia IgE) to normal dogs.[4] Demonstration of passive transfer by the Prausnitz-Kustner test confirms the functionality of canine anti-Malassezia IgE.[4] In addition, Western immunoblotting of sera from dogs with MD has identified several candidate allergens produced by *M. pachydermatis* that are recognized by atopic dogs.[5] Atopy patch testing has not yet been reported in dogs, utilizing yeast extracts. However a T-cell mediated event is supported by the finding that peripheral blood mononuclear cells isolated from atopic dogs with MD also exhibited significantly increased blastogenic responses to *M. pachydermatis* extracts, as compared to those isolated from normal dogs.[6]

The routine clinical identification of hypersensitivity by practitioners requires that a commercial allergenic extract be used for intradermal testing at the optimal concentration for detecting true sensitization. The optimal concentration of an allergen (also known as the "threshold") is the highest concentration that fails to produce a reaction in 90% of normal individuals, but that is capable of identifying a significant number of clinically allergic individuals.[7, 8] Ideally, the threshold concentration should also correctly identify at least 90% of sensitized individuals, although this is difficult to assess due to lack of a validated gold standard. Testing with an allergen at a concentration above the threshold may result in nonspecific false positive ("irritant") reaction. To date, a validated in-vitro commercial assay for anti-Malassezia IgE has not been reported in the scientific literature. Because of great discrepancies in results reported by research laboratories, any commercial offering of an ELISA for detection of anti-

Malassezia antibodies in canine serum should be scrutinized carefully by sound scientific methods before it can be recommended for routine use.[2]

A commercial *M. pachydermatis* extract is available for intradermal testing and subcutaneous immunotherapy (Greer Laboratories, Lenior, NC, USA). This allergenic extract is available in 20,000pnu/ml and 40,000pnu/ml concentrations. A study conducted in healthy dogs with normal skin and dogs with AD (both with and without overt MD based upon cytological evaluation), have demonstrated a threshold concentration of 1,000pnu/ml for use in intradermal testing.[2] This extract is now included in the battery of allergens used for intradermal testing in the author's (DOM) group practice, for evaluation of dogs with a clinical diagnosis of AD.

The *M. pachydermatis* extract produced by Greer Laboratories has been evaluated in a multicenter single-arm proof-of-concept study, with the goal to determine its utility as an immunotherapeutic agent. Atopic dogs that had been on allergen-specific immunotherapy for a minimum of 12 months, but which continued to have chronic/recurrent MD and required antifungal prophylaxis, were enrolled. A total dose of 2,000pnu was administered weekly by subcutaneous injection, and cases were followed for 12 months. Although data from all member study sites were not collated, it is clear from 4 cases enrolled at the author's practice that it can be clinically effective. Two of 4 dogs had an excellent response with resolution of pruritus, discontinuation of maintenance antifungal therapy, and negative cytology, while the other 2 improved enough that the owners elected to continue with immunotherapy. Personal communication with clinicians at other study sites (A. Yu, Guelph, Ontario, Canada, L. Sauber, Tulsa, OK) suggests that this has also been the case at other study sites.[9]

ANTIFUNGAL THERAPY

The antifungal regimen chosen for therapy of Malassezia dermatitis or otitis should be based upon the distribution of the infection, the general health status of the patient, and expectations of the pet owner in regards to time and effort commitment (relevant to topical therapy) and side-effects (most relevant to systemic therapy). Diagnosing and eliminating (or controlling) underlying diseases are also paramount to long-term prevention of recurrence. Since *Malassezia pachydermatis* is part of the normal cutaneous microflora, complete elimination of the organism is likely to be impossible. Please see table 1 for specific doses for the systemic therapy options.

TREATMENT OF MALASSEZIA OTITIS (CAT AND DOG)

Appropriately treating yeast otitis externa is dependent upon appropriately cleaning the ear and choosing an effective ear cleanser and medicated ear drop. Cleaning the ear allows for removal of exudate to allow ear medications to be more effective, can change the environmental pH so it is less suitable for yeast overgrowth, and some ear cleaners even have antifungal effects, such as Epiotic® (Virbac) and DermaPet Skin/Ear Cleanser® (DermaPet).[10,11] Medicated ear drops are typically utilized in Malassezia otitis cases, with two weeks of treatment typically recommended, optimally with a follow up recheck to evaluate if additional therapy or change in therapy is needed.

Many antifungal otic preparations are available on the market and include miconazole, clotrimazole, thiabendazole, and nystatin. The authors agree that miconazole appears to be the otic treatment of choice.

In cases of Malassezia otitis media, oral therapies as outlined for treatment of Malassezia dermatitis are typically utilized in addition to topical therapy, and it is usually recommended to perform an anesthetic ear flush to clean out exudate and infection in the middle ear.

TOPICAL THERAPY OF MALASSEZIA DERMATITIS (DOG AND CAT)

Many topical agents are used to kill Malassezia organisms, including selenium sulfide, enilconazole, miconazole, ketoconazole, clotrimazole and chlorhexidine. A review article revealed strong evidence only for the shampoo combination miconazole/chlorhexidine (Malaseb®), although further studies are needed to elucidate the true efficacy of some of the other topical products. [12]

These topicals are typically used for localized infections, as adjunctive therapy to oral systemic treatment, and prophylactically for prevention of future infections. These medications are available in different forms such as shampoos, leave on conditioners, wipes, and sprays. Bathing recommendations vary with practitioner, but it is not uncommon to recommend once-twice weekly topical therapy, and up to daily if using the leave on conditioners. Selenium sulfide containing shampoos should be avoided in the feline.

SYSTEMIC TREATMENT OF MALASSEZIA DERMATITIS IN THE CANINE

Ketoconazole, itraconazole, fluconazole and terbinafine have all been found to be effective for Malassezia dermatitis. Neither lufenuron nor griseofulvin have been found to be effective treatments for Malassezia dermatitis, and therefore SHOULD NOT be used. Ketoconazole (Nizoral®, Jannsen) and itraconazole (Sporonox®, Jannsen) 5mg/kg/day are very effective treatments. Many cases will need initial treatment duration of 14 to 21 days, while others may require additional alternate day or daily therapy for another 14 to 21 days. Because itraconazole stays in the stratum corneum for a prolonged period of time, pulse therapy can be employed. One study found that dogs treated with 5mg/kg/day for 2 days followed by 5 days without treatment for 3 cycles (i.e. 3 weeks) responded just as well as dogs who received the medication at 5mg/kg/day for 21 consecutive days.[13]

Fluconazole (Diflucan®, Pfizer) and terbinafine (Lamisil®, Novartis) are two other options for patients with Malassezia dermatitis. The dose for fluconazole typically used is 2.5-5mg/kg/day, while the dose for terbinafine is 30mg/kg.day. Fluconazole use has greatly increased in recent years due to drop in price and wide safety margin, and it appears to be a safe and effective treatment. However, anecdotal evidence suggests that it is not as clinically effective as the other azoles in some cases. Terbinafine has become generic, and has used it successfully in a handful of cases that have not responded to or didn't tolerate the azoles.

Regardless of which oral treatment is started, recheck in 2-3 weeks prior to the medication running out is recommended to assess treatment efficacy.

The main side effect of all these medications is gastrointestinal, but the azoles can cause adverse reactions in the liver, drug reactions and have serious drug interactions. The medications are metabolized by the P450 liver enzyme, and will therefore interact with other medications metabolized by the same system (such as cyclosporine). In one study, 7.5% of patients treated with a dose of ≥10mg/kg/day of itraconazole developed a drug induced vasculitis. Due to these reasons, caution should be taken before using these medications in dogs with history of liver disease, and it is generally recommended to check bloodwork in aged or debilitated dogs prior to using.

It should be noted that it is recommended to administer ketoconazole, itraconazole capsules, fluconazole and terbinafine with food. It is recommended to administer liquid itraconazole (Sporonox®) one hour before or two hours after a meal for optimal absorption. Typically compounded itraconazole liquid is not as effective as Sporonox® liquid.

SYSTEMIC TREATMENT OF MALASSEZIA DERMATITIS IN THE FELINE

Because of concerns over gastrointestinal upset and hepatotoxicity, ketoconazole should be avoided in cats. At this time, there is limited information about treating Malassezia dermatitis in cats with terbinafine, although its successful use has been reported in the treatment of dermatophytosis in cats.

Fluconazole and itraconazole tend to be safe, well tolerated and effective in the treatment of Malassezia dermatitis in the cat. Itraconazole tends to be the antifungal of choice, although fluconazole is being used with more frequency due to its safety and inexpense.

PULSE THERAPY

If the infection is recurrent and the underlying disease can not be determined or controlled, anecdotal reports indicate that pulse therapy with ketoconazole, itraconazole or fluconazole can be effective. Doses and frequencies are determined on a case by case basis depending on the symptoms of the patient.

TABLE 1: SYSTEMIC DRUGS FOR TREATMENT OF MALASSEZIA DERMATITIS AND OTITIS MEDIA

Drug	Medication availability	Dose/Frequency/Duration	Species
Ketoconazole	200mg tablets	5-10mg/kg q daily x 21-28d, or (low dose regimen) 5mg/kg qd x 10d, then Eod x 10 Pulse dose regimen for prophylaxis: 5-10mg/kg 2 consecutive days/week	D D D
Itraconzole	100mg capsules or 10mg/ml elixir	5mg/kg q daily x 21-28d, or, 5 mg/kg 2 days/week x 3 weeks	D & C D
Fluconazole	50, 100, 150, 200mg tablets; oral powder for 10mg/ml suspension	2.5-5mg/kg q daily x 21-28d	D & C
Terbinafine	200mg tablets	30mg/kg q daily x 21-28d 30-40mg/kg q daily x 21-28d	D C

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MYSTERY CASES WITH DR. MASON

CASE #1: "ROSCO"

Signalment:

4 year old male, tan Rhodesian Ridgeback X.

Presenting Complaint:

Rosco was presented with recurrent ear infection and itchy pododermatitis.

History:

Age of onset of symptoms was 1 year of age and has been almost continuous since then.

Itching is mild to moderate and occurs at the same time as the ear infection. It is non-seasonal and manifested as head shaking, intense foot chewing and licking with scratching and rubbing.

Dietary manipulation of commercial hydrolysed chicken elimination product has not improved the symptoms.

Previous treatment has included a miconazole, prednisolone and polymyxin ear lotion which initially helped the ear infection and the itchy skin had previously responded to prednisolone 0.5mg per kg per day; however it does not seem responsive now.

Gastrointestinal disease history revealed intermittent upsets.

Appetite is normal and drinking is rated by the owners as normal.

Ectoparasiticide prevention has been a tablet containing lufenuron, milbimycin, praziquantel monthly and occasionally frontline topspot.

Rosco has been treated for a pyoderma with Cephalexin as well in the past.

Examination:

T= 38.0 degrees C, P= 108 bpm, R= 20 bpm, Weight= 39.4kg. Rosco is bright and alert.

Skin findings include; Primary lesions of erythema and papules and some pustules affecting the ventrolateral trunk and all feet.

Ear findings include; Erythema and oedema of both canals. The right pinna and vertical canal had ulcerations and the horizontal canal full of black purulent material.

The tympanic membrane was present on the left side and may not be intact on the right due to difficulty in visualization and pain.

Eye findings include: A mucopurulent discharge from the right eye.

Differential Diagnoses:

Diagnostic Tests:

Plan of Action and Treatment:

Final Diagnosis:

Treatment:

Comments/Follow-up:

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CASE #2: "SALLY"

Signalment:

Approximately 10 years old, female spayed Border Collie X - an animal rescue case.

Presenting Complaint:

A malodorous scaly itchy dermatitis with severe balding.

History:

Sally was impounded 1 ½ weeks ago by the RSPCA. Sally was considered to be in poor condition was under weight and had a chronic itchy skin condition that had not received adequate attention. The previous history was unavailable but the skin and poor condition was judged to be of long standing nature. Since impounding, Sally was very itchy and had a voracious appetite and a water intake that was considered slightly above normal.

Physical Examination:

T= 39.8 degrees F, P= 110 bpm, R= 40 bpm, Wt= 19Kg.

Demeanour was very quiet but alert, responsive and with a stoical gentle, a long suffering but sweet, temperament. Body condition was judged to be poor at 2/5 (with 5 the ideal). The appetitive was ravenous and water intake high.

Skin findings include; No obvious primary lesions. There was extensive truncal total alopecia with lichenification, scale and hyperpigmentation. Although the limbs were spared the complete alopecia, scale and hyperpigmentation and partial patchy alopecia was present, with erythema and papules.

Ear findings include; A bilateral scaly hyperpigmentation, erythema and swelling with narrowing of both canals. The canals were very waxy with a yellow-green purulent discharge in the horizontal canal. The tympanum was obscured with the discharge.

Eye findings include; A bilateral mucopurulent discharge.

Differential Diagnoses:

Diagnostic Tests:

Diagnosis:

Treatment:

Outcome and Prognosis:

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CASE #3: "SUAK"

Signalment:

5 year old neutered female, Alaskan Malamute.

Presenting Complaint:

Suak was presented with generalized smelly, scaly, pruritic dermatitis.

History:

Suaks itchy skin problem had developed gradually over the last few years. It may have been intermittent and mainly a summer issue but now non seasonal. Previous treatment had been a benzoyl peroxide shampoo last used 1 week ago and a prednisolone neomycin topical ointment used as needed Antibiotic tablets containing clavulanic acid and ampicillin may not have helped. Suak had been on several weight loss diets and allergy elimination diets to no avail.

The owners contended she was picky eater; water was available continuously from a horse trough Injection of long acting cortisone each few months stimulated the appetite but latterly did not help the skin itch. The last Depo-Medrol was >5 months ago. The owners reported that Suak was sulking as she had been locked out of the house because of the smell hair and scale shedding, so she no longer played with the kids.

Physical Examination:

T= 37.9 degrees C, P= 80 bpm, R= 20 bpm, Weight= 55kgs.

Sauk was very lethargic and sedate. The body condition score was 8 out of 5 (5 ideal).

The mucous membranes are pink and moist with CRT < 2 seconds. Hydration appeared to be adequate. There is moderated dental tarter. On the ventral lateral thorax skin lesions were large and small round to arcuate shaped hyperpigmentation and alopecia. There is a generalized seborrhoeic waxy dermatitis and otitis.

Differential Diagnoses:

Diagnostic Tests:

Diagnosis:

Treatment:

Comments/Follow-up:

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MYSTERY CASE #4: "TOOKY"

Signalment:

7 year old entire male, West Highland white terrier.

Presenting Complaint:

Tooky was presented with odiferous generalized scaly pruritic dermatitis.

History:

Tooky's skin problem had developed gradually over the last few years. Initially just red itchy skin with intermittent itching that was more progressive than seasonal, as reported by the owners. They report that various shampoos had limited effect. A tablet of prednisolone in combination with a antihistamine used with antibiotic tablets containing clavulanic acid and ampicillin may not have helped.

Physical Examination:

T= 38.0 degrees C, P= 120 bpm, R= 20 bpm, Weight= 11kgs.

The body condition score was 5 out of 5 (5 ideal).

There is a generalized seborrhoeic waxy dermatitis and otitis with a generalised erythema scale and patchy alopecia.

Differential Diagnoses:

Diagnostic Tests:

Diagnosis:

Treatment:

Comments/Follow-up:

NOTES

BEHAVIORAL MEDICINE AND ITS ROLE IN DERMATOLOGY

Landsberg GM[1]
[1]North Toronto Animal Clinic, Thornhill, ON

Is it behavioral or is it medical

A simplistic approach to diagnosis would be to look at the behavioral presenting signs to determine whether they have a behavioral cause or a medical cause. For example, acute and chronic stress and situations of frustration and conflict can lead to signs of self-trauma or increased grooming behaviors, while any medical condition causing pruritus can also lead to self-directed behaviors. However in actuality there are far more than two simple options. Self directed behaviors that are initiated by a behavioral cause often develop secondary medical problems including pain, inflammation and infection. Whether the cause is behavioral or medical the pain and discomfort of self-trauma can increase anxiety and irritability. Even if the initiating medical problem is resolved the self directed behavior can persist due alterations in neuroreceptors and neurotransmitters, residual neuropathic pain, or owner responses that have reinforced the behavior or increased the pets stress and anxiety.

The interplay between health and behavior is further complicated by the fact that stress may play a role in inducing inflammatory skin diseases in humans and animals. This has been referred to as the brain skin connection since studies have documented that stress activates immune cells in the skin which can initiate, perpetuate or exacerbate underling skin diseases such as psoriasis, atopic and irritant excema and rosacea.1 For example, it has been demonstrated in murine studies that stress can cause a state of immune alertness, which may alter skin homeostasis and induce immune dermatoses.2 Therefore even when there appears to be a purely medical etiology addressing any underlying behavioral issues may be an important component for successful treatment and reducing recurrence.

Stress and its effects on health and behavior

Stress impacts on both health and behavior through its effects on the HPA axis and activation of the noradrenergic system.3 Stress is an altered stated of homeostasis which can be caused by physical or emotional factors that trigger psychological, behavioral, endocrine and immune effects that are designed to handle stress. 3 In cats, a transient hyperglycemia may also be seen. When stress is persistent or chronic there is continued stimulation of the HPA axis and an increase in cortisol with depression of the catecholamine system, leading to alterations in the immune system and the possible development of stress related diseases. A recent study found higher plasma levels of dopamine and 5HT in pets with stress compared to controls.4 Increases in dopamine may enhance aggressive behavior and lead to an increase in stereotypic and grooming behaviors. Prolactin levels may also be elevated in fearful and anxious pets.5 In one study, higher prolactin levels were found in dogs with chronic stress, stereotypic behaviors, fear aggression and autonomic signs, while lower levels of prolactin were associated with acute fearful and phobic events.6 Therefore, there can be marked differences in the effects of acute and chronic stress on health and behavior which impacts on both diagnosis and treatment.7

In humans and pets there may be a correlation between stress and poor health, poor immune function, cardiovascular disease, asthma, gastrointestinal and urogenital disorders, skin disease, behavioral disorders as well as aging. Cats with feline interstitial cystitis, have altered bladder permeability and an increase in plasma norepinephrine.8 Treatment with multimodal environmental enrichment (MEMO) and Feliway have both been found to improve not only feline interstitial cystitis but also respiratory disease, inflammatory bowel disease, fearfulness, nervousness and aggression.9,10 In humans, stress and anxiety can alter bacterial flora, inhibit gastric emptying, increase colonic activity, and increase intestinal permeability leading to irritable bowel syndrome, gastrointestinal reflux, stress induced hypersensitivity, and heartburn. Similarly stress and anxiety in pets can cause anorexia and hyperexia, diarrhea, vomiting and colitis.11 In cats prolonged anorexia can have serious hepatic consequences. Pica, polyphagia, and polydypsia may also be stress induced.

Stress may also contribute to immune dermatoses in humans by activating immune cells and increasing cutaneous lymphocyte-associated antigens in the skin. In humans stress has also been shown to result in an increase in cytokines, release of opioids, serotonin and other vasoactive peptides, and decreased HPA axis responsiveness in atopic individuals.12,13 Stress may also contribute to an increase in epidermal permeability.14 Opioid peptides may further potentiate pruritus. In pets, stress, fear and anxiety have also been associated with a shortened lifespan and increased severity and frequency of dermatologic disorders. 15

Finally conflict, frustration, and stress may cause or contribute to the development of a wide range of behavioral signs and behavior disorders including altered sleep wake cycles, inappropriate elimination, excess vocalization, destructive behaviors, fears, phobias, anxiety disorders, panic and displacement behaviors and stereotypic and compulsive disorders (discussed below).

Behavioral signs as an indicator of physical health

Monitoring and assessing behavioral signs is a critical component of every veterinary visit. Virtually any medical condition can present with behavioral signs and behavioral signs may be the first indicators of disease. Behavioral signs can also be used to monitor improvement or response to therapy. Therefore to insure early diagnosis and intervention, owners should be asked about behavior problems at each visit and pet owners should be encouraged to seek guidance as soon as signs arise.

Is it behavioral or is it dermatologic – making the diagnosis?

Dermatologic disorders that might have a behavioral cause include self-directed and self-traumatic behaviors as well as feline hyperesthesia. The challenge for the practitioner is to rule out any underlying medical problem that might be a cause or contributing factor. As discussed the role of stress, conflict, frustration and anxiety must be considered not only as a potential cause of the signs, but as possible contributing factors (i.e. stress exacerbation of medical signs) or as an inciting factor leading to secondary dermatologic disease. Finally it is possible that an inciting behavioral cause has been resolved leaving an ongoing medical problem or that a medical cause is resolved leaving an ongoing behavior problem. Therefore the presence of skin lesions does not necessarily indicate a medical cause and the absence of lesions does not necessarily indicate a behavioral cause.16 Recent studies (not yet reproduced) have identified elevated serum cholesterol, HDL and LDL, concentrations in dogs with tail chasing and in another study 24% of dogs with compulsive disorders had a mildly elevated hematocrit.

Diagnosis begins with determining whether the pet has a medical or behavioral condition or both. Therefore, in addition to the medical evaluation, the behavioral history must be thoroughly evaluated in each case to determine if there were any changes at the onset of the problem, whether the pet's behavioral needs are being addressed, whether there are ongoing stressors, and how the owner has responded to the behavior. Signalment, including sex, age and breed is also an important diagnostic consideration.

Displacement behaviors

Displacement behaviors which might include self-trauma, tail chasing, spinning and hyperesthesia may be initiated by situations of conflict and frustration, especially in pets that are genetically predisposed and in those that anxious or highly aroused and therefore less able to settle (achieve behavioral homeostasis). Conflict is when the pet is motivated to perform two opposing behaviors (e.g. approach and withdrawal). Frustration is when the pet is motivated to achieve a goal but unable to do so. Displacement behaviors that arise in response to a specific stimulus (e.g. visual, auditory, odor, tactile) or event (e.g. car ride, veterinary visit, owner departure or homecoming) usually resolve when the inciting factors are removed. However secondary medical problems such as pain, pruritus and infection may be a maintaining or perpetuating factor.

Compulsive disorders

Compulsive disorders are those in which the displacement behaviors are exhibited independent of the original context. The behaviors have no apparent goal and have an element of dyscontrol in either the initiation or termination of the behavior. They may be repetitive, exaggerated, sustained or so intense that they might be difficult to interrupt. Although stereotypies might be a coping mechanism leading to a reduction in arousal, they become compulsive when they persist even after the anxiety evoking situation

is resolved. Compulsive disorders can affect both physical and mental health. Initiating factors can (in a pet that is genetically predisposed) be repetitive or recurrent situations of conflict or frustration or an environment where the pet does not receive sufficient outlets and opportunities for its normal repertoire of behaviors (i.e. vacuum activities). In a study in Brazil of 20 dogs with psychogenic ALD, most were large breed dogs and all were described as having an anxious personality. None of the owners played with their dogs routinely, and 70% were never walked. Specific triggers included loss or death of a canine companion, acquisition of a new pet, or changes in theh household.17 Compulsive disorders might be a) self-directed behaviors such as acral lick dermatitis and flank sucking in dogs, psychogenic alopecia, hair pulling, scratching and face pawing in cats, and tail chasing including self-mutilation; b) neurological, hallucinatory and locomotory signs such as air snapping, pacing, spinning, pouncing, rhythmic barking, freezing, staring and chasing objects (real or imaginary) in dogs and staring, predatory sequences and hyperesthesia in cats; and ingestive signs such as picas, licking, polyphagia, and polydypsia in dogs, and wool or fabric sucking in cats There appears to be a genetic predisposition to the development of some stereotypic behaviors (e.g. wool sucking in oriental breeds of cats, spinning in Bull Terriers, tail chasing in German Shepherds). In fact, a canine chromosome locus has recently been identified for flank sucking in Dobermans.18

It is possible that there is a common pathophysiology; that neurotransmitters vary between presenting complaints; or that there is changing involvement as the problem progresses. Locomotory compulsive disorders tend to develop after repeated conflict, are displayed most commonly in situations of high arousal, and are often so intense that it may be difficult to calm the dog or interrupt the behavior. Oral compulsive behaviors may develop more acutely and are most likely to be displayed in situations of minimal stimulation. Hallucinatory type behaviors such as fly snapping and fixed staring may involve differing pathophysiologic mechanisms.

Beta-endorphins, dopamine, and serotonin have all been implicated primarily based on evidence of response to therapy. Dopaminergic drugs such as amphetamines may induce stereotypies and narcotic antagonists may block the resposne.19,20 Some compulsive disorders may be mediated by opioid receptors, particularly in the early stages, since opioid antagonists such as naltrexone have been successful at reducing “stereotypies”.20,21 Altered glutaminergic neurotransmission may also be a factor in the pathogenesis, in which case blocking glutamate sensitive NMDA with drugs such as memantine or dextromethorphan may be an effective treatment option.22,23 Abnormal serotonin transmission has also been suggested to be the primary mechanism by which stereotypies are induced. Based on human models for the treatment of OCD, drugs that inhibit serotonin reuptake (e.g. clomipramine, fluoxetine) have been shown to be most effective in the treatment of canine and feline compulsive disorders and animal studies have identified direct evidence of serotonin involvement.24-26 (See notes on behavioral drugs)

Differentiating Dermatologic from Compulsive

Medical differentials include diseases that lead to pain or pruritus (e.g. hypersensitivity reactions, neuropathies), infections (e.g. bacterial, fungal, parasitic), endocrinopathies, tumors, or skin disorders associated with systemic diseases (e.g. hepatocutaneous syndrome). When there are no primary lesions, medical and behavioral causes may be particularly difficult to differentiate. In a study of 21 cases referred to our behavior service for psychogenic alopecia, 76.2% had a medical etiology, 9.5% were compulsive and 14.3% were both medical and behavioral. A combination of adverse food reaction and atopy was the most common diagnosis. Some cats with histologically normal skin had a purely medical cause.16 For acral lick dermatitis, food intolerance, deep pyoderma which may be multidrug resistant and a variety of other medical causes including tumors, trauma, protozoal and fungal infections have all been implicated. Nail biting in dogs may also be a displacement behavior or compulsive disorder, but immune, inflammatory or infectious causes including Malassezia must first be ruled out.

Tail mutilation, facial oral pain syndrome and hyperesthesia in cats are a challenge to determine whether there is a medical or behavioral cause or some combination of both. Feline oral facial pain syndrome may present with repetitive chewing and licking behaviors as well as pawing and self mutilation. Feline hyperesthesia may be due to dermatologic disease; neurologic and painful diseases including partial complex seizures, spinal diseases and neuropathies; FeLV induced myelopathy, compulsive disorders and any condition leading to behavioral arousal. Clinical signs may include dilated pupils, twitching skin, rippling along the back, excessive grooming, biting and licking, and behaviors of high arousal including anxiety, aggression, restlessness, running, and vocalizing. Studies have also found that in some cases pain pathways may be overly sensitive to relatively innocuous touch sensations.27

Treatment of Compulsive Disorders

Behavioral management combined with drug therapy is required for the successful control of most compulsive disorders. In addition, addressing underlying behavioral issues and drugs to reduce anxiety may be needed for those medical problems in which there stress and anxiety are contributing or concurrent factors. In humans, psychotherapy has been used successfully to improve cases of intractable inflammatory dermatoses.28 Pets with compulsive disorders, should receive a more structured and stimulating daily routine that provides outlets for all of the pets behavioral needs, while training should focus on reinforcing what is desirable and NOT punishing what is undesirable. Some pets may be particularly sensitive to inconsistency or lack of predictability in their daily schedule or in their interactions with their owners. Therefore the daily routine should include regular sessions of social interaction with people (in the form of training, play and exercise) or with other pets. Owners might be encouraged to focus on play that simulates the normal activities of the species or breed, (e.g. pulling carts, retrieving, mousing). Following social interaction and training, scheduled periods of inattention may help the pet learn to expect and accept spending time alone. At these times it may help to calm the pet by having a favored bedding area where a variety of enrichment toys are provided (feeding, chew and manipulation toys. In fact working for some or all of the daily food either through training or by stuffing or filling feeding toys is an important component of treatment for most compulsive disorders.

Training should encourage behaviors that are desirable. Owners that train with a combination of reinforcement and punishment are likely to contribute to the pet's conflict and unpredictability. Casual and inconsistent owner interactions should be replaced by a program of predictable rewards where the owners insure that all rewards including affection, toys, and food are only given for behaviors that are incompatible with the compulsive disorder such as resting on a mat or playing with a favored toy (response substitution). Clicker training can help to more immediately reinforce desirable. A leash and head halter for dog or a harness for cats can be used to prompt the desired response as well as to inhibit, disrupt or prevent undesirable behavior so that the undesirable behavior is neither punished or reinforced.

Concurrent drug therapy is generally required in conjunction with the behavior therapy and in some pets may be the primary focus of treatment. Clomipramine or an SSRI such as fluoxetine are usually the first drugs of choice for compulsive disorders in dogs. See notes on behavioral drug therapy.

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NOTES

DRUGS USED TO TREAT BEHAVIORAL DERMATOSES AND THEIR ACTIONS

[1]Landsberg, G
[1]North Toronto Animal Clinic, Thornhill, ON, northtorontovets.com

Overview

Psychotropic drugs and natural alternatives are primarily indicated for reducing signs associated with phobic, panic or chronic anxiety states and to improve trainability especially in situations where the pet is too anxious, fearful or impulsive to learn. Since these problems may cause or contribute to dermatologic signs such as tail chasing, self trauma or hyperesthesia, they may be an integral component of a comprehensive treatment program. Drugs may also have a dramatic effect when there is behavioral pathology such as in compulsive disorders and impulse dyscontrol; but for the most part, drugs help to reduce the anxiety or arousal that might be contributing to the problem. Psychotropic drugs are also effective in the treatment of urine marking in cats and as an adjunct to behavior therapy in treating some forms of aggression but this paper will focus on the use of drugs for reducing underlying anxiety and in the treatment of self traumatic disorders. Some of these drugs are not truly psychotropic drugs, although they may have behavior quieting effects. These include NMDA antagonists such as memantine, amantadine, dextromethorphan and the opioid antagonist naloxone as well as drugs that may alleviate signs of neuropathic pain and/or seizures including gabapentin, carbamazepine, levetericetam and phenobarbital. In addition, some psychotropic medications may be used for the treatment of self-trauma because they have multiple modes of action such as the use of amitiptyline or doxepin for their antihistaminic effects or tricyclic antidepressants such as amitiptyline or nortriptyline for neuropathic pain. However, drugs do not change the relationship with the stimulus so that concurrent behavior modification will also be needed to desensitize, countercondition and train alternative desirable responses.

Evidence based decision making should be used to provide the best treatment option for the pet, owner and problem. However, many sources of veterinary information fall into the poorest level including personal experience, colleague opinion, text books, continuing education, inconclusive studies, the net and in vitro research or research from another species. The most desirable evidence is from systematic reviews with homogeneity or randomized controlled clinical trials (RCT). In the case of veterinary behavioral drugs, much of the information has been extrapolated from human literature; however, drug metabolism and receptor effects vary between species. This can lead to inaccurate assumptions with respect to dose, duration of effect, contraindications and side effects. Therefore, drugs that are licensed for pets (e.g. clomipramine, fluoxetine) should first be considered since they have data with respect to safety, efficacy, side effects, contraindications, toxicity and pharmacokinetics. Some of the drugs used in veterinary neurology and pain management such as phenobarbital, potassium bromide, levetiracetam, gabapentin, dextromethorphan, clonazepam or clorazepate have also been studied so that onset of effect, duration of effect, dose or toxicity has been at least in part established for pets.

Antidepressants

Antidepressants cause little or no sedation and are unlikely to inhibit learning or memory. There is extensive evidence on the efficacy of the tricyclic antidepressant (TCA) clomipramine and the selective serotonin reuptake inhibitor (SSRI) fluoxetine for treating anxiety disorders and compulsive disorders. Clomipramine and fluoxetine are licensed for the treatment of separation anxiety in dogs, and clomipramine is licensed in other countries for compulsive and anxiety disorders in dogs, and in Australia for feline urine marking. While antidepressants reach peak plasma levels within hours of dosing this does not reflect their therapeutic effect since reuptake inhibition may induce down-regulation of postsynaptic receptors. Therefore, while improvement may seen within the first 1 to 2 weeks, 4 to 8 weeks of therapy is generally recommended to fully assess therapeutic effects. Side effects may include gastrointestinal signs including inappetance, lethargy, and neurological signs such as tremors or seizures. Compared to SSRI's, TCAA's are of greater concern in pets with seizures. TCA's and SSRI's should not be used concurrently with MAO inhibitors such as selegiline and amitraz, other antidepressants or narcotics. Serotonin syndrome is a serious and potentially fatal concern from excess serotonin which is most likely

to arise with high does or when drugs that increase serotonin are combined such as St. Johns Wort, Paanx ginseng, amphetamines, and possibly tramadol, metoclopramide, or chlorpheniramine. Signs include confusion, shivering, hyperthermia, tachycardia, diarrhea, twitching, tremors, seizures, and coma.

TCA's such as clomipramine and amitriptyline block the reuptake of serotonin and to a lesser extent noradrenaline. The degree of serotonin and noradrenaline reuptake blockade, as well as anticholinergic, antihistaminic and alpha adrenergic effects varies between TCA's. Clomipramine is the most selective inhibitor of serotonin reuptake of the TCA's and is therefore the most appropriate TCA for the treatment of compulsive disorders. It inhibits noradrenaline reuptake and has mild anticholinergic and antihistaminic effects which might account for its side effects, such as lethargy, gastrointestinal upset or dry mouth. TCA's are contraindicated with glaucoma, cardiac disease, or where urine retention is a concern. However, clomipramine is associated with less urinary stasis and anticholinergic effects in dogs compared to humans. At therapeutic doses in dogs clomipramine and amitriptyline do not alter cardiac rate or rhythm.1 Clomipramine and amitriptyline may be useful in controlling underlying anxiety, and reducing fear and impulsivity. However, evidence based studies on the efficacy of antidepressants other than clomipramine are lacking Clomipramine in combination with a behavior modification program (BMP) is an effective treatment for separation anxiety and is licensed for this use.2,3 Studies have also shown clomipramine to be an effective treatment for compulsive disorders in dogs and cats.4-8 Amitriptyline has moderate effects in inhibiting both serotonin and noradrenaline reuptake, strong antihistaminic and anticholinergic effects and is used as adjunctive treatment for neuropathic pain. Doxepin has marked antihistaminic effects but minimal effects on serotonin reuptake and moderate effects on noradrenergic reuptake. Tricyclic antipressants may also be used in combination with other anxiolytic agents. For example benzodiazepines may be used on an as needed basis along with the ongoing use of a TCA for stress evoking events such as owner departures, thunderstorms, veterinary visits or at times when self traumatic disorders are most likely to be exhibited. In one study clomipramine in combination with hehavior modification and alprazolam as needed was effective for the treatment of storm phobias.9 Tricyclic antidepressants such as amitriptyline and nortriptylinne may also be used in combination with drugs such as gabapentin for the treatment of neuropathic pain. 10

SSRI's are selective in their blockade of the reuptake of 5HT1A into the presynaptic neurons. Because they are selective for serotonin reuptake they may have fewer side effects than TCA's, including less cardiac effects and hypotension. They may be preferable where urine retention, increased intraocular pressure, sedation or anticholinergic effects might be a concern. Paroxetine is mildly anticholinergic. In dogs, SSRI's are most often used for the treatment of separation anxiety and compulsive disorders, as well as for the treatment of phobias, fear and anxiety and impulse control disorders.4,7,11-15 Since the clearance half life of fluoxetine is 6.2 hours and 49 hours for its active metabolite norfluoxetine gradual weaning is generally not required. However, when the drug is used for longer than 8 weeks, it might be prudent to consider a gradual weaning. Its primary side effect is decreased appetite which may resolve with decreased dose. Since SSRI's inhibit cytochrome P-450 enzymes they can lead to increased toxicity if combined with drugs that are metabolized by these enzymes. Extrapolating from humans fluoxetine, paroxetine and sertraline might inhibit the metabolism of dextromethorphan, theophylline, antipsychotics, propranolol, diazepam and alpazolam.

Anxiolytics

Buspirone and benzodiazepines may be associated with increased aggression due to disinhibition.

- Buspirone, an azapirone, is a serotonin (5HT1A) receptor agonist and a dopamine (D2) agonist. Buspirone has been used for mild fear and anxiety. It is non-sedating, does not stimulate appetite, and does not appear to inhibit memory. It takes a week or more to reach effect and is therefore not useful for situational anxieties. Higher doses may have more immediate effect. Adding buspirone to an SSRI or TCA might help to insure an adequate serotonin pool.

- Benzodiazepines potentiate the effects of (GABA), an inhibitory neurotransmitter. They cause a decrease in anxiety, hyperphagia, and muscle relaxation. They reach peak effect shortly after each dose and can be used alone or in combination with other drugs for situational anxieties on an as needed basis. Since clonazepam, oxazepam and lorazepam have no active intermediate metabolites they may be safer when hepatic function is compromised. Benzodiazepines need to be dosed frequently and there may be a rebound effect if withdrawal is not gradual. They can cause paradoxical excitability and can have an amnesic effect. They are useful for counterconditioning since they decrease anxiety and increase appetite; however, diazepam has been reported to cause rare cases of fatal hepatotoxicity in cats.16
- Beta blockers such as propranolol have been used to reduce the physiologic signs of anxiety in combination with drugs that diminish behavioral signs.17 By blocking beta adrenergic activity, physical signs of anxiety (increased heart and respiratory rate, trembling, gastrointestinal upset) are decreased.

Trazodone

Trazodone has been reported to be useful in the treatment of anxiety in dogs primarily as an adjunctive treatment to other behavioral medications such as SSRI's, TCA's and benzodiazepines. It is a serotonin 2A antagonist-reuptake inhibitor (SARI). Since trazodone may be useful in helping to induce sleep and to calm anxious pets it might be added on an as needed basis prior to stressful events.18

Anticonvulsants

Anticonvulsants may be used when the clinical signs (e.g. spinning, tail chasing, hyperesthesia) might be caused by a seizure or partial seizure. In one study of spinning bull terriers neurological abnormalities were identified in all 7 dogs and 5 responded to phenobarbital.19 Since complex partial seizures may be indistinguishable from compulsive disorders, a therapeutic response trial may warranted. Temporal lobe (limbic) epilepsy may present with mood alterations, hallucinatory behavior, self-traumatic behavior or bouts of aggression associated with ictal, postictal or even interictal stages. Phenobarbital has been used alone or in combination with other behavioral drugs (e.g. benzodiazepines, propranolol) for behavioral calming and quieting prior to a stressful or phobic event (e.g. veterinary visit, thunderstorm) or perhaps on an ongoing basis. Potassium bromide has also been used in the treatment of sleep disorders. Levetiracetam is an antiepileptic drug that is gaining increased use in veterinary neurology. In humans it was the first drug approved for partial epilepsy and is also used for other neurologic and psychiatric disorders including anxiety, stress, panic, mood disorders and Tourettes.20 Gabapentin has been used in combination with SSRI's for the treatment of impulse control disorders and noise phobias. Because it is effective for neuropathic pain, it is used in combination with other behavior and pain control drugs for self-traumatic disorders. Carbamazepine may act as a mood stabilizer and antidepressant. In humans it is used for epilepsy related aggression, aggression with agitation, anxiety, and irritability, and for impulsivity and neuropathic pain.

Selegiline is an MAOB inhibitor which enhances catecholamine transmission. While it is used in North America for cognitive dysfunction syndrome, in Europe it is used for the treatment of "emotional disorders". In one study dogs with chronic stress and high anxiety associated with stereotypic and displacement behaviors, fear aggression, and autonomic signs had high prolactin levels, while dogs with acute fears and mild phobias had lower prolactin levels. Therefore selegiline might be more effective for dogs with chronic stress while fluoxetine would be more effective in dogs with acute anxiety.21 In one study, selegiline combined with propranolol, alprazolam and a behavior program was effective for social and sound phobias.17 In a comparative study, selegiline and alpha-casozepine appeared to both significantly improve anxiety and emotional disorders of dogs.22

Drug therapy for compulsive disorders and hyperesthesia

Beta-endorphins, dopamine, and serotonin have all been implicated. Dopaminergic drugs such as amphetamines may induce stereotypies and narcotic antagonists may block the resposne.23,24 Another possibility is that compulsive disorders are mediated through opioid receptors, particularly in the early stages, since opioid antagonists such as naltrexone have been successful at reducing "stereotypies".24,25 Abnormal serotonin transmission has also been suggested to be a mechanism by which stereotypies are induced. Based on human models for the treatment of OCD, drugs that inhibit serotonin reuptake (e.g. clomipramine, fluoxetine) have been shown to be most effective in the treatment of canine and feline compulsive disorders and animal studies have identified direct evidence of serotonin involvement.4-8,14,15,26 Clomipramine or fluoxetine (or most other SSRI's) should be the first drugs of choice for compulsive disorders in dogs and cats. TCA's other than clomipramine are not sufficiently selective for serotonin reuptake blockade and are therefore not used for the treatment of compulsive disorders. However, in addition to effects on mood and anxiety, TCA's such as doxepin and amitriptyline have strong antihistaminic effects and may reduce neuropathic pain associated with self trauma.

Altered glutaminergic neurotransmission may also be a factor in the pathogenesis and that blocking glutamate sensitive NMDA may be an effective treatment option. In one case series, memantine, an NMDA receptor antagonist reduced the severity of compulsive disorders in 64% of 11 treated dogs within 2 weeks of treatment.27 Memantine may be effective alone or may have a synergistic effect when combined with fluoxetine.28 Amantadine and dextromethorphan may also be useful because of its NMDA antagonist properties.29 However due to its short half life, rapid clearance and variable absorption in dogs, dextromethorphan may not be a reliable form of therapy.30

Tail chasing and self trauma in pets, feline facial pawing and scratching and feline hyperesthesia may have both behavioral (e.g. compulsive) and medical (e.g. complex partial seizure, neuropathic pain) diagnoses. In fact, for tail chasing efficacy has been reported in clinical studies using fluoxetine, clomipramine, naloxone, memantine (alone or in combination with fluoxetine), dextromethorphan, and, in spinning bull terriers, with phenobarbital.4,5,15,19, 25, 27,29,31,32 Other drugs that might be effective alone or in combination include buspirone, pheromones or natural supplements (discussed below) to reduce underlying anxiety; an SSRI or clomipramine plus gabapentin along with lorazepam as needed for hyperesthesia; drugs that relieve pain (some of which also have behavioral effects) such as tramadol, opioids, meloxicam, gabapentin, amitriptyline, carbamazepine, naltexone, memantine, amantadine and dextomethorphan; and drugs that might have an effect on temporal lobe epilepsy or partial complex seizures such as phenobarbital, potassium bromide or levetiracetam.

Dosing and compliance

Since many owners cannot administer medications, they are being reformulated into compounded liquids, flavored tablets and transdermal medications. However, once compounded the medication may be altered or less stable. In addition, to date, there has been no data to support the efficacy of transdermal medication for behavior drugs in cats. One study found that the bioavailability of transdermal doses of fluoxetine was 10% compared to oral dosing.33 In another study systemic absorption of both amitriptyline and buspirone was poor compared to the oral route.34

Natural products and supplements

"Natural" products can have great variation in quality, level of activity, and efficacy. Adverse effects, toxicity and contraindications have yet to be established and there are very few efficacy studies.

Pheromones bind to pheromone binding proteins that are specific to that species. The feline cheek gland pheromone (F3) serves to mark out boundaries and provide emotional stability. Synthetic F3 pheromone may be effective in reducing marking and anxiety such as when introducing cats into new environments. DAP is a synthetic version of the intermammary appeasing pheromone in the lactating bitch. Its function is to calm and reassure the offspring. In conjunction with behavior therapy a DAP diffuser may help to reduce fear and anxiety in the home, while a DAP collar may be useful in reducing anxiety both indoors and out.

Melatonin is derivative of serotonin and may inhibit dopamine. Melatonin has been reported to be useful as a sleep aid and for canine fears and phobias.

Tryptophan when added to a reduced protein diet was shown to lower territoriality scores while high protein diets without tryptophan were associated with greater aggression.35 Adding tryptophan to an SSRI or TCA therapy may help insure an adequate serotonin pool.

L-theanine may reduce signs of anxiety in both dogs and cats including noise phobias, travel anxiety, urine marking and fear aggression.36,37

Alpha-casozepine is a hydrolyzate of a protein in cow's milk. In one study it was equally effective as selegiline in reducing anxiety in dogs.22 In a placebo controlled study in cats, it significantly improved fear, fear of strangers, contact with familiars, fear related aggression and autonomic signs.38

Other natural compounds for which there is little or no data on efficacy for behavior therapy in pets include St. John's Wort (sedative and antidepressant effects in humans), DHA, Eleutherococcus (Siberian ginseng); Panax ginseng; Passionflower (Passiflora); skullcap; hops; valerian and kava kava. However, a recently released combination of Marigold officinalis and Phellodendron amurense (Harmonease) has shown some efficacy in reducing anxiety. Aromatherapy with lavender or chamomile may have some efficacy in reducing anxiety.39 Topical application of lavender oil on the pinna of a dog's ear may stimulate vagal activity and lower heart rate which may have a calming effect.40 Other treatment modalities (e.g. acupuncture, homeopathy) are beyond the scope of this paper but there is little or no data yet available to support their efficacy.

Drug doses for behavior therapy

	Dog	Cat
Alprazolam	0.01-0.1 mg/kg bid to qid	.125 -.25 mg/cat sid – tid
Clonazepam	0.1-1.0 mg/kg bid-tid	.02-.2 mg/kg sid-bid
Clorazepate	0.5-2 mgkg prn to tid	0.2- 1 mg/kg sid-bid
Diazepam	0.5-2 mg/kg prn (e.g. q 6h)	.2-.5 mg /kg bid to tid
Lorazepam	.025-.2 mg/kg sid to prn	.025-.05 mg/kg sid-bid
Oxazepam	0.2-1 mg/kg sid-bid	.2 - .5 mg/kg sid to bid
Amitriptyline	2.0-4.0mg/kg bid	.5 -1 mg/kg sid
Clomipramine	1-2 mg/kg bid	.3 - .5 mg/kg sid
Doxepin	3-5 mg/kg bid – tid	.5-1 mg/kg sid - bid
Nortriptyline	1-2 mg/kg sid to bid	.5- 2 mg/kg sid - bid
Fluoxetine	1.0 – 2.0 mg/kg sid	.5-1 mg/kg sid
Paroxetine	1 mg/kg sid	.5 to 1 mg /kg sid
Sertraline	1-4 mg/kg sid or divided bid	0.5 -1.5 mg/kg sid
Propranolol	0.5-3.0 mg/kg bid or prn	.2 – 1 mg/kg tid
Buspirone	0.5-2.0 mg/kg sid-tid	.5 to 1 mg/kg bid
Trazodone	2-5 mg/kg prn to 8-10 mg/kg bid-tid	
Memantine	.2-1.0 mg/kg bid	
Amantadine	3-5 mg/kg q 24h	3 to 5 mg/kg q 24h
Dextromethorphan	2 mg/kg tid -qid	.5-2 mg/kg tid
Carbamazepine	4-8 mg/kg bid to tid	2-6 mg/kg sid-bid
Phenobarbital	2.5-5 mg/kg bid	2.5 mg/kg bid
Gabapentin	10-30 mg/kg tid (seizure dose) 2-10 mg/kg bid-qid (pain)	5-10 mg/kg sid–bid (seizure dose) 2-5 mg/kg bid (pain)
Potassium bromide	10-35 mg/kg daily or divided bid	Not recommended
Levetiracetam	20 mg/kg tid (seizure control)	20 mg/kg tid (seizure control)
Selegiline	0.5-1 mg/kg sid	0.5-1 mg/kg sid

References available from author on request

NOTES

THE SENSIBLE DERMATOLOGIC PHARMACY – MERGING MEDICINE WITH MANAGEMENT

Dermatology patients often require medication long term, in many cases lasting for the life of the pet. We have excellent products available for dispensing, but we also have seen a lot of competitive pressure lately, not only from internet pharmacies, but also from retail stores and human pharmacies. Are human generic drugs a welcome relief, or should we be relying on products developed and tested for use in the species we are treating? With veterinary clients having more opportunities than ever before to purchase medications for their pets, it's time for veterinarian to consider how to best utilize their pharmacies.

Does It Make Sense to Stock and Dispense Human Generic Medications?

Generic human drugs serve a purpose, but most of these drugs that veterinarians stock are not approved by the US Food and Drug Administration for use in animals, may come in inconvenient dose sizes, may have directions and cautions appropriate for humans rather than animals, and are tested for equivalency only against branded human medications. From a business standpoint, these products are similar to or the same as those sold by pharmacies, department stores, and other retailers, often for considerably less. Unfortunately (or fortunately, depending on your perspective), those same retailers are locked in a bitter battle for customers, in some instances reducing the price of many human generic drugs to a few dollars for a month's supply. Some are even providing these products for free (including prescriptions for pets).

You may be able to sell these products more cheaply than branded medications, but you cannot profitably sell them as cheaply as low-price retailers. What do you say when clients ask what the difference is between the human generic that you think you are selling cheaply, and the truly cheap human generics available elsewhere? The other option is to continue selling human generics and hope that clients don't notice that the same products are available elsewhere at significantly lower prices, despite the millions of dollars that retailers spend to promote these bargains. At the same time, pet owners are being conditioned to expect that human generics are the treatments of choice for many animal ailments--probably an unintended endorsement by the veterinarians dispensing them.

Human generics do have their place, but if the goal is to deliver medications to owners at fair and competitive prices, and you believe that a human generic is in the best interest of a patient, then the sensible solution is to write prescriptions for these products and allow owners to find the best bargain they can (and there are plenty to be found). When it comes to an analysis of profitability from human generics, they only remain profitable as long as clients are unaware of the alternatives. That is not a sustainable business model. In addition, profits tend to be marginal at best when markups are applied to inexpensive medications. So, if you have a human generic that costs you a few pennies apiece and you double or even triple that to arrive at a retail price, you have a very meager return for something the client still could have purchased cheaper elsewhere.

From a business perspective, it makes the most sense to stock veterinary-labeled products for sale and price them appropriately. Such products are FDA-approved and tested in animals for safety and efficacy, come in dose formulations that are convenient for the species being treated, and are manufactured by companies that will stand behind the products if there are problems or adverse events and also that support the industry in which you work. That should be a compelling argument. After all, what have human generics companies done for you lately?

What About Internet Pharmacies?

Most veterinary practices are very concerned about Internet pharmacies, but these companies only exploit the sometimes-unrealistic drug pricing models used by some veterinarians. Veterinarians are occasionally surprised to learn that most of veterinary pharmaceutical manufacturers do not sell product directly to these pharmacies. Often, non-veterinary Internet pharmacies purchase product from veterinarians (often referred to as "diverters"), who purchased those products from manufacturers or distributors. Of interest, though, is that even when paying these diverting veterinarians a commission for buying these products on their behalf, Internet pharmacies may still be able to price the products less than veterinarians who price according to standard markups in use by the profession today. Why is that? It's because Internet pharmacies are selling commodities according to a competitive retail pricing model, while some veterinarians continue to try to price these products as if they were professional services.

The Veterinary Pharmacy as Profit Center

To operate a pharmacy as an efficient profit center, veterinarians need to be able to manage inventory and price products appropriately. There are very real costs associated with inventory. There is the direct cost of acquisition, which is the price paid for the medication itself, as well as the indirect costs associated with ordering and stocking products. Indirect costs can constitute 20% to 45% of the acquisition price,[1] depending on how efficiently the pharmacy is being managed.

The most challenging issues regarding pharmacy vulnerability are pricing models, and this is usually complicated further by the tendency to pay commissions to pharmaceutical sales associates. There are three basic pricing models in use today by veterinary practices: markup, margin, and community pricing.

Markup is the most common, and it is not unusual for veterinary hospitals to mark up their products 100% to 200% to arrive at a retail price, typically doubling or tripling (or something in between) the acquisition cost of the medications, and then adding a dispensing fee.[1] This magnitude of markup is extreme by retail standards, and paying a professional commission on top of that only compounds the problem of trying to close the gap between veterinary prices and those of competitors.

Markups have another unfortunate consequence--they tend to amplify the cost of expensive medications (or treatments intended for large dogs), and reduce the costs of inexpensive medications (or those used in small dogs or cats).

For practices that see an inequality in the markup model, margin (also known as cost-plus) models are a good alternative. Veterinarians already use this premise on a simple level in the sale of pet food. They implicitly realize that they can't double or triple the cost of a bag of pet food if they want the owners to purchase the food without asking a lot of awkward questions. The margin approach involves adding a unit price to each item rather than a markup formula. In addition, practices rarely pay professional commission on the sale of pet foods or they would never be able to keep the price competitive.

We can do something similar for all pharmaceuticals, including tablets, capsules, shampoos, and injectables, which is profitable for the practice, and fair to the clients, regardless of the size of their pets or the cost of the medication itself. This involves adding a "margin" or base amount to products (or services) that does not vary with the cost of the drug or the size of the animal. For margin pricing, take the actual unit cost of the drug and add an acceptable amount to cover the costs of ordering, storing, and loss (either as a fixed amount, a variable amount, or as a percentage of the actual cost of the product). At this point, there is full cost recovery, but no profit. To include profit, add a unit or

margin charge on what the practice wants to earn for each unit dispensed or administered. This allows the practice to make a standard "margin" on every product sold, while covering all acquisition and inventory costs. There is no penalty for a pet owner who needs to buy a large quantity of or very expensive medication. It is possible to pay commission to associates on the basis of margins, but only on the margin amount itself and not the full retail price, since all but the margin represents expense, not profit.

Community pricing is a way to establish a selling price on the basis of what others charge. A practice might use community pricing based on other veterinary hospitals in the area or on retail prices available at Internet pharmacies or other outlets. Community pricing ensures that you won't be readily undersold, but unless costs are determined, you may still be stocking and dispensing medications that are not profitable for the hospital.

As has already been demonstrated, it is not possible for veterinarians to run a profitable pharmacy for a sustained period selling products that can be purchased elsewhere at lower prices.

The Importance of Customer Service

When clients present a pet for examination, they are prepared to pay professional fees to the veterinarian for the expertise in medical care, diagnostic testing, and treatment recommendations. After all, providing medical care to an animal requires a high level of expertise that isn't available from other sources, and veterinarians deserve to be well compensated for their professional skills. However, once the veterinarian has made a recommendation for treatment, the client has concluded the professional part of the visit and then needs to purchase the products recommended at the best combination of price and convenience available. Most clients will pay a slight premium to purchase the medication in the veterinary office, but they consider it a commodity and not something to which professional fees should be attached. Large discrepancies in prices can cause owners to be concerned that if drugs are overpriced by the practice, prices for services at the practice might be inflated as well. Since veterinary services are a relative bargain for pet owners, this is not the type of message a practice wants to convey.

It is very important that veterinarians not judge a client's desire to save money as disloyalty to the practice. After all, when they get a prescription from their physician, they may very well compare prices at different pharmacies, including online and even out-of-country pharmacies. Once again, pet-owning clients paid the professional fees to the veterinarian for the medical advice--as far as they are concerned, the purchase of the medication is just a commodity transaction. It probably has nothing to do with how they feel about the care their pet received, and many are shocked to see veterinarians react in a threatened fashion when they ask if the same or equivalent medication might be available online or at a retailer. Don't be threatened or respond defensively; it adversely affects the client's perception of you as their pet health advocate and is an overreaction to an honest question.

Clearly, the goal is to select the most appropriate medication for the disorder, for the practice to make a reasonable profit on stocking and dispensing medications, and for clients to receive value for their pharmaceutical purchases and even more value for medical services and counseling. This might involve changes to the current pharmaceutical pricing models currently used by most veterinary practices (and potentially adjusting professional production compensation for associates), stocking products labeled for use in the species to which they are to be administered, communicating appropriately about the benefits and risks of all medications dispensed, and serving as an advocate for the needs of clients and pets. Some additional considerations include:

- Advocate pet insurance, to help owners better afford needed medications
- Consider providing your own Web-based pharmacy if clients find this convenient
- Provide reminders to clients to administer medication on schedule, especially those that are only periodically administered (such as heartworm and flea-control products)
- Use injectables when medically prudent to do so, to improve compliance and convenience
- Maintain a practice formulary to keep inventory lean and to avoid duplication
- Monitor product turnover and stock products according to need and use
- Expect professional compensation for professional services and retail revenue for commodity transactions.

Summary

The veterinary pharmacy is at an important crossroads, and nowhere is this more acutely evident than in the situation of dermatology patients, in which lifelong medications are often required. The retail marketplace is becoming extremely competitive, and new models and approaches need to be considered for the profession. Success is likely predicated on veterinarians acting in their best interest and stocking products that are veterinary labeled rather than human generics and pricing those products competitively. Will veterinarians heed the call to action?

Reference

[1]. Ackerman L, ed. Blackwell's Five-Minute Veterinary Practice Management Consult. Ames, IA: Blackwell Publishing; 2007.

Recommended Reading

American Animal Hospital Association. Financial & Productivity Pulsepoints, 5th ed. Lakewood, CO: AAHA Press; 2008.

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NOTES

EFFECTIVE MARKETING FOR DERMATOLOGY SERVICES

Introduction

Marketing is the process of planning and executing the development, pricing, promotion and distribution of goods and services, with the purpose of achieving practice goals. By anticipating and satisfying the wants and needs of the consumer and referring practices, products and services flow from the practice to the pet owner.

Marketing sometimes gets a bad reputation amongst veterinarians, but there is nothing immoral or unethical about meeting the health care needs of patients. In fact, in these days of heightened awareness of compliance, it might well be considered unethical for practices not to make their clients aware of products and services for which pets and primary-care practices may benefit.

Marketing is not about selling unwanted services, but is a method of meeting the needs of primary-care practices and pet owners, by informing them of what they should be doing for their pets and how the specialty practice can help meet those needs. Today's marketing is about developing long-term productive relationships with clients. Specialty practice is a customer-oriented business philosophy that stresses customer satisfaction as the key to achieving practice goals.

External Marketing

External marketing is the process of attracting new clients to the practice. The purpose of this is to either "grow" the practice, make up for client loss through attrition, or to increase market visibility. In any marketing plan, the main source of new clients is often referral from existing clients.

Prior to creating a marketing plan, it is usually a good idea to have an independent evaluation of the practice by an operational practice expert. It can be devastating to start a marketing program only to have it fail because the practice is not really poised to take full advantage of the effort. Operational on-site assessments help to anticipate issues that need to be addressed, and that would otherwise impede the progress of the marketing effort.

Internal Marketing

Internal marketing directs marketing efforts towards existing clients, while external marketing efforts target new clientele. To be effective, a marketing plan must address both concerns. Future growth in veterinary practices comes from increased utilization of services from those existing primary-care practices as well as the entry of new clients to the practice. Dramatic gains can be made in many practices simply by providing needed information to the public and to existing clients. Traditional "selling" need not be part of a professional marketing plan.

Internal marketing deals with promoting services to existing clients. Existing clients are already a well-defined population whose healthcare predilections are easily accessible. Marketing to existing clients is both medically necessary and cost effective.

Marketing is not about selling; it is about educating. Veterinarians need to inform clients about the proper ways of caring for their pets, and often need help in this regard from referral practices.

Database Management
Effective marketing requires knowledge of the practices and pets being served and a way to measure compliance. Whether the system is computerized or manual, if the information is not available in the records, then it is hard to use it productively for marketing efforts.

The practice must be able to track this information and direct client educational materials to those owners who have been notified but have not yet acted. The information of what services are outstanding for any individual animals and primary-care practices must be available as a central resource, not just buried in the medical records.

Target Marketing
With a solid database of information on pets, target marketing is a very effective form of internal marketing. Target marketing identifies pets or primary-care practices that have similar needs, and customizes an offering to meet those needs. The promotional piece can be written to specifically "target" the defined group, both because the need is similar and because this allows personalization of the message. Messages that are personalized and speak to a defined need are most likely to be regarded seriously and acted upon.

Cautions
Marketing is about education and delivering value. In veterinary medicine, this can be accomplished at the same time as generating a reasonable professional profit. However, it is important to ensure that the reasons for the marketing have to do more with value creation than with revenue generation. If clients can understand the value in a process then they appreciate the professionalism and care behind the recommendation. If they cannot understand the value in an offering, then it can have a negative impact on trust and compliance.

Miscellaneous
Marketing should not involve selling clients services that lack intrinsic value. For most veterinary practices, internal marketing should focus on delivering those services, which the hospital team already believes is valuable, but which is not currently being delivered in a reliable fashion. Consultants refer to this as "low-hanging fruit". Whereas veterinarians may be tempted to buy expensive equipment that can be marketed to clients, there are so many routine services that are not being consistently delivered and that warrant increased attention by practices.
Today's clients are value shoppers, and it is critical that veterinary practices invest in future growth through effecting marketing campaigns. In this competitive environment, it is important to differentiate one practice from another, and one must be able to demonstrate how one's practice provides value relative to its differentiation.

Recommended Reading:
Ackerman, L: Five-Minute Veterinary Practice Management Consult, Lippincott, Williams & Wilkins, 2007.

Ackerman, L: Business Basics for Veterinarians, ASJA Press, New York, 2002

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NOTES

OPINIONS ON ALLERGEN-SPECIFIC IMMUNOTHERAPY: WHAT MATTERS?

Kimberly Coyner, DVM DACVD
Dermatology Clinic for Animals, Las Vegas NV

VARIABLES OF ASIT[1]:

Protein concentration of maintenance ASIT
- Typical 10,000 - 20,000PNU/ml; Range 1000 - 40,000PNU/ml

Protein concentration per allergen
- 1000 - 10,000PNU/ml

Allergen dose injected
- Typical 1ml; Range 0.05 – 1ml

Frequency of injection
- Typical every 21 days; Range every 3 – 31 days

Numbers of allergens treated
- Typical 10 or less, up to 40
- One vial vs. multi-vial allergen set

Mold allergens
- Included vs. not included in treatment
- If included, mix with other allergens vs. use separate vial

TYPICAL ASIT INDUCTION SCHEDULE:
- Protocols vary; induction set usually consists of 2-3 vials of increasing allergen concentration, ie. 200, 2000, and 20,000PNU/ml
- Usually loading protocols with increasing allergen doses given q 2-4 days
- Maintenance allergen dose usually reached in 4-6 weeks, and after 10-15 injections

DERMATOLOGY CLINIC FOR ANIMALS PROTOCOL:

Protein concentration of maintenance ASIT
- 20,000PNU/ml; Range 5000 – 20,000PNU/ml

Protein concentration per allergen
- 1000 - 2,000PNU/ml

Allergen dose injected
- Typical 1ml; Range 0.05 – 1ml

Frequency of injection
- Typical every 14 days; Range every 3 – 31 days

Numbers of allergens treated
- Typical 20 or less, up to 40 ; more than 20 allergens are separated into a 2 vial allergen set
- Allergens to include determined by seasonality of symptoms, exposure history, strength of reaction, cross reactivities, etc

Mold allergens
- Included vs. not included in treatment depends on clinical signs/seasonality, number/strength of mold reactions; if included, usually use separate vial

Induction schedule

- In most animals, start with 20,000 PNU/ml vial, 0.10 – 0.25ml first dose, increasing by 0.25ml once weekly until maintenance dose of 1.0ml given q 2 weeks; rush protocol occasionally done.
- In cats and very small dogs, a 10,000 PNU/ml vial is dispensed for the first 4 injections before the 20,000 PNU/ml vial is started, and the maintenance dose is usually 0.5 – 0.75ml q 2 weeks.
- Maintenance allergen dose is usually reached in 4-6 weeks after 4-6 injections.

RESULTS OF CLIENT QUESTIONNAIRE:

- 69 questionnaires returned
- 88% on immunotherapy at least 6 months
- 75% still on immunotherapy
- 47% receive allergen weekly, 47% receive allergen q 2 weeks
- 25% discontinued immunotherapy, 9 due to poor response or exacerbation of symptoms
- 30% would be less willing to perform immunotherapy using traditional induction schedule
- 78% patients improved at least 50%
-

CONSIDERATIONS:

- Owner compliance is a major factor in success of ASIT; in published studies, up to 49% of owners discontinued therapy without consulting the clinician or were lost to follow-up.[2]
- 30% of owners responding to our questionnaire reported they would have been less willing to give immunotherapy induction injections using standard protocols; is the typical allergen induction schedule using 2-3 dilutions given q 2-4 days really necessary in veterinary medicine, or could it lead to increased owner drop – out?

References:

1. Griffin CE, Hillier A. The ACVD task force on canine atopic dermatitis (XXIV): allergen-specific immunotherapy. Vet Immunol Immunopathol 2001: 81; 363-383.
2. Loewenstein C, Mueller R. A review of allergen-specific immunotherapy in human and veterinary medicine. Vet Dermatol 2009: 20; 84-98.

AUDIENCE PARTICIPATION:

1. Allergens per vial
    a. I keep less than or equal to 10-12 allergens per vial
    b. I do not limit the number of allergens per vial

2. Minimum protein concentration per allergen in a treatment vial
    a. 500PNU/ml
    b. 1000PNU/ml
    c. >1000PNU/ml

3. Allergens per pet
    a. I hyposensitize with 10-12 allergens or less
    b. I do not limit the number of allergens I will use in hyposensitization

4. If a pet reacts to numerous allergens on allergy testing, I will prescribe a 2 vial set
    a. Yes
    b. No

5. I often include molds in ASIT
    a. Yes
    b. No

6. Molds are always placed in a separate vial from pollens
    a.Yes
    b. No

7. Induction schedule
    a. I use a 3 vial induction schedule
    b. I use a 2 vial induction schedule
    c. I use a one vial induction schedule

8. Rush Immunotherapy
    a. Performed frequently in my clinic
    b. Performed rarely in my clinic

9. Typical maintenance allergen frequency
    a. Once a week
    b. Every 2 weeks
    c. Every 3 weeks
    d. Every 4 weeks

10. Typical maintenance allergen concentration
    a. 10,000PNU
    b. 20,000PNU
    c. Other

11. When are the patients first rechecked after starting immunotherapy?
    a. 2-4 weeks later
    b. 6-12 weeks later
    c. 16-24 weeks later d. Other

NOTES

OPINIONS ON ASIT – WHAT MATTERS?

Stephen L. Lemarie, MS, DVM, Dipl. ACVD
Southeast Veterinary Specialists
Metairie, Louisiana

PATIENT SELECTION/PATIENT PREPARATION

- Age
- Breed
- Duration of clinical signs
- Concurrent disease
- Geographic history

TESTING METHOD

- Intradermal skin testing
- In vitro/serology
- Combination

ASIT COMPOUNDING

- In house – DVM more involved
- Reference lab – DVM not involved or involved to a lesser degree
- Antigens per vial
- Final concentration of maintenance vial

INDUCTION PROTOCOL

- Traditional 3 vial
- Traditional 2 vial
- Rush Immunotherapy

MAINTENANCE PROTOCOL

- Concentration
- Interval
- Antigen manipulation
- Keeping up with your ASIT patients

NOTES

OPINIONS ON ASIT - WHAT MATTERS?

Gram WD[1]

INTRODUCTION: Allergen specific immunotherapy (ASIT) is an effective means of controlling allergic patients. Increased efficacy is associated with "fine tuning" of the ASIT protocol. My thoughts on "What Matters" are derived from 20 years of experience gained in private practice, academics and as a consultant in the industry. I have practiced in 3 different countries and multiple climatic zones with the majority of my allergy tests being "skin test" rather than "serum tests." I am also consultant for Greer Laboratories with the primary duty of helping general practioners with questions regarding ASIT. In an average year, I either actively manage or consult on approximately 2,000 patients receiving allergen specific immunotherapy. The majority of my allergy clients are seeking a cost effective means of controlling their pets' symptoms. Although, I can be opinionated, I do not feel that my opinion is the ONLY correct opinion and appreciate open discourse. I feel vulnerable articulating when, how and why I utilize ASIT, but that is what has been asked of me.

DETERMINATION OF CANDIDATES FOR ASIT:

A) Diagnoses of Atopy (or in rare cases allergic respiratory disease).
B) Presence of symptoms for more than 3 months out of the year, or anticipation of symptomatic progression (predisposed breed).
C) Medical control may be limited in "special cases:" Diabetes/pancreatitis if steroids; Seizures if antihistamines; Neoplasia if Boxer or Golden; Excess of "safe annual steroid use."
D) Ask myself, what is the best treatment for this patient today, tomorrow, next week, next month, next year, and 3-5 years from now.

I view ASIT as the best means for long term control of Atopy and prefer intervention early in the course of the disease. It can be adjusted on a seasonal basis or even daily if needed. Due to the length of time that may lapse while waiting for ASIT to become effective and the general desire to use as low of a dose of all forms of therapy (including ASIT), additional medical therapy will likely be necessary in the short term or intermittently. Intermittent exacerbations may require intermittent medication use. I view my duty, to both treat the patient as well as educate the caregiver. The best analogy that comes to mind is educating parents regarding monitoring and managing a child's asthma or diabetes.

FORMULATION OF ALLERGENS AND CONCENTRATION: We do formulate our own ASIT. Typically, most of our allergens are stored at concentration of 40,000pnu. Upon selection for inclusion, it is diluted to 20,000pnu and placed into a vial (10ml) which will contain the final formulation of all selected allergens. By convention, we would like to limit our included allergens to 10 and thus include 10 equal (1.0ml) portions of allergen (20,000pnu concentration). Often, the included allergen number may be increased to 20 for a patient with a large number of positive test results. In this case we would likely include 0.5ml of each allergen. Variations of this protocol commonly occur. When trying to include important allergens in patient with a large number of significant reactions, many factors are considered. Due to likely cross reactivity amongst grasses, I may make a mix of smaller volumes of important grasses. Due to a relatively short tree pollen season, I may leave trees out of formulation completely and instead utilize allergens that would be present year round. Following the concept of summation of effect and threshold, I may consider it more important to include dust mite allergen than a specific tree allergen for a patient that flares in the spring and fall but has equal reactions to trees, weeds and dust mites. I also sometimes consider the strength of the positive reaction as well as the time of the year that testing was performed. I do feel that there are seasonal increases in reactivity of allergens that would be present in higher numbers at that time of the year. Occasionally, we may need two separate mixtures of ASIT. This may be pursued initially or after a utilizing the initial mixture for a year or more. As I side note, I very rarely include flea allergen, but recently have begun to often include malassezia.

FREQUENCY OF ALLERGEN INJECTIONS: Maintenance immunotherapy is tailored to the needs of each patient and client. Client communication is paramount. Approximately 40% of our patients receive 1.0cc every 14 days, while another 40% receive 0.5cc every 7 days and the remaining 20% receive 0.25-1.0cc every 3-31days. If a patient's symptoms consistently flare a few days before the scheduled injection is due to be administered, the injection is given early at the full dose. If that protocol is beneficial, the dose is then tapered for cost efficiency purposes. I do believe that client compliance (and therefore patient care) is better with weekly injections than biweekly injections. Interestingly, I do have some clients who misunderstand the initial "build up" protocol and may administer 1.0cc every 3 days for several months. Most of these patients seem to do better during the initial phase than those following the more routine protocol. For routine patients, If all goes well after a year or two, the injections may be tapered to 1.0cc once a month. If no flare is noted after a year of this protocol, the ASIT may be discontinued. However, I find that some of these do eventually flare up again and restart the ASIT. I also find that early intervention with ASIT seems to be associated with a higher success rate.

SUCCESS RATES: We are in the process of reviewing our patient success rate for the 4th time in almost 20 years. Once again, I apologize for a lack of "good scientific evaluation." However, this is the "how I do it." The medical records of patients placed on the initial ASIT protocol 12-13 months previously are reviewed. Only those patients receiving the immunotherapy for the entire duration are included in the evaluation. The clients are asked "how the patient is doing with regards to the ASIT. General groups include: A) "Very Well" (minimal other medication is needed compared to the previous year), B) Well (better than previously, but still require somewhat regular "mild" medical therapy- mostly antihistamines, frequent baths), C) No improvement, D) Worse. No statistical analysis has been performed. Pets deemed to have successfully responded were assessed by the clients as doing either "Very Well" or "Well." The success rates have been as follows: 1992=75%, 1995= 90%, 2000= 87% and 2009= %. Virtually never is the answer "Worse." While the initial success rate of 75% correlates well with other studies, I feel the higher success rate noted in succeeding years is like due to several factors. Prior to opening the practice, clients would have to drive approximately 4 hours to see a dermatologist and many of my patients in the 1992 study had been symptomatic for many years while the symptoms advanced and/or steroids were used chronically. This was actually before antihistamines and fatty acids were commonly used in my practice area. It was also before malassezia was a routine diagnosis and before modern advances in flea control were widespread. Gosh, I did not even have an internet connection. Now I feel very old! However, later, while listening to a lecture by Dr. Eddy Rosser (who practices in Michigan), he also quoted approximately a 90% success rate and we began talking. It seems that he too had been "fine tuning" the dose a frequency of ASIT injections as discussed under the "Frequency of Allergen injections" heading.

SUMMARY: ASIT should be considered as an option earlier in the course of the disease process than many people consider, and may result in permanent amelioration of symptoms. With individualized protocol adjustments, ASIT has few side effects, is often more convenient than oral or topical therapy and offers a cost effective means of controlling allergic patients.

1. The University of Edinburgh**,** Division of Veterinary Clinical Sciences**,** The Royal (Dick) School of Veterinary Studies**,** Easter Bush Veterinary Centre**,** Roslin**,** Midlothian EH25 9RG Scotland Practice: Animal Allergy and Dermatology PC, Richmond and Virginia Beach, 1100 Eden Way North Suite 101c, Chesapeake, VA 23320

NOTES

FELINE DERMATOLOGY – CATS ARE NOT SMALL DOGS – PART 1: THE DRUGS

Lowe AD[1]
[1]Fox Valley Animal Referral Center, 4706 New Horizons Blvd, Appleton, WI 54914

INTRODUCTION

Cats are one of the most important species in companion animal medicine, accounting for $7.1 billion of annual expenditures in veterinary medicine in the USA[1]. Despite this, for many of the drugs which we use in veterinary medicine, feline-specific pharmacokinetic studies are unavailable and generalizations must be made from studies performed in other species. Important differences exist in the manner in which cats handle many drugs. This lecture will focus on some of these important differences with specific reference to drugs used in the field of dermatology.

GENERAL DIFFERENCES

Cats may show altered absorption of drugs due to differences in the anatomy of their gastrointestinal tracts. Cats have simple, shorter gastrointestinal tracts than either people or dogs, and adjust for this with slower intestinal transit times and, in some cases, higher drug permeability[2]. Food significantly slows gastric emptying and intestinal transit time in cats. This may lead to decreased oral absorption of poorly soluble drugs, which require dissolution, when these medications are given to cats on an empty stomach[2]. It is important to pay particular attention to feeding guidelines, when available, for dosing of oral medications in cats.

Cats also differ from other species in their metabolism and excretion of many drugs. A major difference is the relative deficiency of the enzyme glucuronyl transferase in cats compared with humans or dogs. This enzyme is responsible for phase II glucuronoconjugation reactions. These reactions help to convert lipophilic molecules into more water soluble molecules which can then be excreted from the body. Lower levels of glucuronyl transferase in cats result in decreased clearance and prolonged elimination half-lives of certain drugs[3]. The classic example of this is acetaminophen, which is poorly tolerated in cats. Acetaminophen is seldom used in veterinary dermatology, however the antibiotic chloramphenicol is also metabolized through glucuronoconjugation and has decreased clearance and increased toxicity in cats[3].

Cats are additionally notoriously difficult for owners to medicate at home. In particular cats have been noted to frequently react to oral administration of metronidazole, clindamycin, and trimethoprim-sulfadiazine, though administration of any oral medication can be a challenge[2]. Oral medications, especially capsules, may also be more prone to lodge in the esophagus of cats than other species. One study documented radiographic evidence of esophageal retention in 53% of cats administered a barium-containing capsule[4]. This is of particular concern with medications such as doxycycline, tetracycline, clindamycin, propanolol, iron supplements and bromide, all of which may cause cause esophageal lesions in cats[2, 3], including esophageal strictures in cats administered doxycycline[5]. Flushing with water after administering these medications orally is important and can help reduce the incidence of these problems[6].

Due to the difficulties with oral dosing in cats there has been interest in the use of transdermal medications. Though there are differences between products, most feline publications show that absorption of transdermal medications is poor, or at best, highly variable[2]. Fluoxetine applied transdermally to cats resulted in bioavailability of only 10% compared to when the drug is given orally. Adjusting the dose of transdermally applied fluoxetine accordingly however can result in similar plasma concentrations[7]. Transdermal methimazole is poorly absorbed in cats[8], though this contrasts with the results of separate studies showing clinical efficacy after repeated transdermal application of methimazole to hyperthyroid cats[9,10]. Amitripyline, buspirone and dexamethasone were all shown to have poor systemic absorption when applied transdermally to cats which is therefore considered an unreliable route of administration[2].

GLUCOCORTICOIDS

Glucocorticoids are possibly the most common class of drugs used in feline dermatology, though again, pharmacokinetic and pharmacodynamic studies are lacking in cats to establish ideal treatment regimens. The doses of glucocorticoids which are recommended for cats may vary and are often based upon a combination of extrapolation from other species and anecdotal clinical experience. It has been noted by many clinicians that cats seem to require higher doses of glucocorticoids than dogs in order to achieve similar clinical effects. This opinion is supported by at least one study which showed that the number of glucocorticoid receptors present in the skin and the liver of cats were approximately half that present in the dog[11]. The affinity of feline glucocorticoid receptors for their ligand was also shown to be lower than in dogs[11]. Doses of glucocorticoids are usually divided into therapeutic ranges, including anti-inflammatory and immunosuppressive ranges. The division between ranges is somewhat arbitrary, but provides a useful starting point when choosing an initial glucocorticoid dose, based upon the condition to be treated. In dogs, typically cited anti-inflammatory doses of prednisolone are between 0.55 to 1.1 mg/kg/day, while immunosuppressive doses range from 2.2 to 4.4 mg/kg/day. Many authors recommend doubling these doses in cats, resulting in anti-inflammatory doses of prednisolone of between 1.1 to 2.2 mg/kg/day and immunosuppressive doses between 4.4 to 8.8 mg/kg/day[12-16]. There does appear to be a difference between dosing with prednisone and prednisolone in cats. While these drugs are considered completely interchangeable in dogs, cats are less effective at absorbing and/or metabolizing prednisone. In a study comparing these two drugs, it was shown that only 21% of orally administered prednisone appears in the blood as prednisolone in cats, indicating prednisolone is the superior choice in cats[17]. Initial studies of glucocorticoids in cats suggested that a circadian rhythm of endogenous cortisol secretion was present and that evening administration of glucocorticoids would most closely mimic this natural secretion[18]. Subsequent larger studies have failed to document such an effect however and it appears that time of day may not be an important consideration with glucocorticoid-dosing in cats[19,20].

Large scale studies of the clinical effects of glucocorticoids on cats are scarce but clinical experience suggests that cats tolerate glucocorticoids very well, with side effects considered less frequent than in dogs[12,21]. In a study of 14 cats administered daily immunosuppressive doses of glucocorticoids for two months only 1 cat developed marked side effects, though mild polyuria and polydipsia (PU/PD) was eventually seen in all cats[21]. This contrasts with the situation in dogs where PU/PD is typically marked when similar doses of glucocorticoids are given and additional side effects such as muscle wasting and hair loss often become apparent within weeks to months[16]. In dogs, glucocorticoids interfere with the release, or action, of anti-diuretic hormone. This results in almost immediate PU/PD and decreases in urine specific gravity[22]. PU/PD is a less commonly observed glucocorticoid side-effect in cats and in several studies occurred only after chronic glucocorticoid administration[21, 23]. Additionally, glucocorticoid-treated cats which develop PU/PD are able to maintain a concentrated urine[21, 23, 24] suggesting glucocorticoids have less effect on the secretion, or action, of ADH than in dogs. It is suggested that the cause of PU/PD in glucocorticoid-treated cats is the result of glucosuria and osmotic dieresis, though glucosuria has not been present in all affected cats[21, 23 ,24].

Glucocorticoids are well known to predispose towards diabetes mellitus due to their antagonistic effects on the action of insulin. Cats are suggested to be more prone to the diabetogenic effects of glucocorticoids than dogs. Combined, controlled studies relative to other species would be required to be definitive, but there is some weak support of this theory from comparing separate studies which showed no changes in blood glucose or glucose tolerance measurements after 28 days of treatment with prednisone at a dose of 1.1 mg/kg/day in dogs[25], whereas cats treated with similar doses of prednisolone (2 mg/kg/d) developed hyperglycemia and impaired glucose tolerance after only 8 days[26]. The hyperglycemia and glucosuria induced by glucocorticoids should resolve in normal cats with drug

withdrawal, however in cases with pre-existing subclinical diabetes mellitus, glucocorticoid treatment may be enough 'push' a patient into a clinical diabetic state which requires insulin therapy. Differences may also exist between glucocorticoids in terms of their propensity to induce diabetes in cats. A pilot study comparing the effects of equipotent doses of dexamethasone and prednisolone in cats showed a greater prevalence of glucosuria in the dexamethasone-treated cats, suggesting it may have a greater diabetogenic effect[27].

Several recent cases series have shown a temporal association between glucocorticoid administration and the development of congestive heart failure (CHF) in cats without pre-existing cardiac disease[28, 29]. The most common glucocorticoid associated with this side effect was methylprednisolone acetate and signs were seen as quickly as 1 day following administration[29]. CHF in affected cats was associated with hypertrophic cardiomyopathy, however, provided cats survived the initial crisis, the hypertrophic changes were observed to resolve over time. Affected cats had prolonged survival times relative to cats with CHF due to other forms of disease[28, 29]. This led the authors to propose that cats may develop a unique form of glucocorticoid-associated CHF[29]. Plasma volume expansion due to the hyperosmotic effect of glucocorticoid-induced hyperglycemia was suggested to be involved[30].

Through their inhibitory effects upon keratinocyte and fibroblast proliferation, as well as upon collagen synthesis, glucocorticoids can cause significant atrophy of the skin. Decreased amounts of epidermal lipids and increased transepidermal water loss also occur, all of which can lead to side effects such as scaling, hairloss, follicular atrophy, bruising and thinning of the skin. These signs appear to be infrequent in cats with commonly used glucocorticoid dosing protocols, though higher doses and longer treatment courses can cause similar signs[21, 23]. When glucocorticoid-induced cutaneous atrophy does occur in cats it can be extremely severe leading to paper-thin skin that may tear either spontaneously, or with only gentle manipulation[23, 24]. Curling of the pinna is another unique, but rare, side effect of glucocorticoid use in cats[21, 23].

CYCLOSPORINE AND AZATHIOPRINE

Though unlicensed for use in the cat, cyclosporine is receiving increasing attention in veterinary dermatology and has proved effective for the treatment of a variety of diseases including feline atopy[31, 32], lesions of the eosinophilic granuloma complex[33], immune-mediated adnexal skin diseases[34], urticaria pigmentosa[35] and idiopathic facial dermatitis of Persian cats[36]. Cyclosporine is rapidly absorbed after oral administration, with similar bioavailability and half-life to that which is seen in the dog[2]. Typically used doses are in the range of 5 mg/kg/day, or 25 mg/cat, when using microemulsified versions such as the veterinary product Atopica. Cats usually tolerate cyclosporine well with the most common side effect being gastrointestinal upset resulting in mild, and sometimes transient, diarrhea in 10-45% of cats[31-33]. No significant changes have been seen in serum biochemistry panels or CBC profiles of cats treated with cyclosporine[31, 33]. There have been several reports of cats receiving cyclosporine developing toxoplasmosis, which has been fatal in some cases[37, 38]. Further work is being performed to quantify this risk. Controversy exists as to whether these cases developed after cats were newly exposed to the parasite, or whether cyclosporine caused recrudescence of previously latent disease[37, 38]. For this reason it is recommended by some authors that, prior to beginning treatment with cyclosporine, toxoplasma titers be performed in cats[37, 38]. Cats with negative antibody titers may be at less risk to develop toxoplasmosis, though this is unclear. A single positive titer indicates only exposure and it is unclear what that ideal decision would be in these cases until we have a greater sense for the magnitude of the risk of cyclosporine-use in cats with both positive and negative pretreatment titers. If cyclosporine-use is chosen for cats with positive titers, it should be with informed consent of the potential risks. It may additionally be worthwhile to repeat the titer in a month to screen for any evidence of rising antibody levels. In all cases, cyclosporine-treated cats should be kept indoors and prevented from eating raw meat to minimize future exposure to the parasite.

Azathioprine is commonly used as a steroid-sparing, immunosuppressive agent in canine dermatology. Azathioprine undergoes complicated metabolism with the primary active metabolite, 6 mercarptopurine (6-MP), being acted upon by three further pathways to generate a variety of intermediates. One important pathway is through the action of the enzyme thiopruine methyltransferase (TPMT), which converts 6-MP to non-toxic products[2]. Cats have low TPMT activity relative to humans and dogs, which may be involved with the profound bone marrow suppression that can occur when cats are administered azathioprine[2]. Azathioprine use is generally discouraged in cats.

ANTIBIOTICS

Several important differences when using antibiotics in cats have already been discussed and include the increased potential for esophageal injury with doxycycline and clindamycin[3], and increased toxicity of chloramphenicol due to poor glucuronoconjugation[3]. Clindamycin and doxycycline should be flushed down with water after dosing, while chloramphenicol use in cats may be best avoided. Oral administration of trimethoprim-sulfadiazine is also associated with excessive hypersalivation in cats[2].

A further important difference with cats is their susceptibility to retinal toxicity with certain fluoroquinolones. Thus far, of the fluoroquinolones licensed for use in cats, there are published reports of this side effect only with enrofloxacin, which has led to the development of a dose-dependent retinal degeneration and acute blindness in some cats. In clinical cases where this side effect has been seen, the dose of enrofloxacin exceeded 5 mg/kg/day in all but one case[2]. In manufacturer studies no signs were noted at 5 mg/kg/day of enrofloxacin, but developed at 20 mg/kg/day or greater[2]. The label for enrofloxacin has subsequently been changed to a maximum recommended dose of 5 mg/kg/day for cats. Retinal degeneration has not been seen with up to twice the highest label dose of orbifloxacin, or five times the highest label dose marbofloxacin, though mild lesions were seen with even higher doses of orbifloxacin[2].

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NOTES

FELINE DERMATOLOGY – CATS ARE NOT SMALL DOGS – PART 2: THE DISEASES

Lowe AD[1]
[1]Fox Valley Animal Referral Center, 4706 New Horizons Blvd, Appleton, WI 54914

INTRODUCTION

Cats suffer from many of the same dermatologic conditions as dogs, though the response of feline skin to these diseases can be quite different. Several unique dermatoses also exist in cats which are not seen in dogs. This lecture will focus on some of the unique manifestations of common feline skin diseases and highlight several less common feline-specific dermatoses.

ALLERGIC SKIN DISEASE

In dogs with allergic skin disease, the most common cutaneous lesions which are seen are those which occur secondary to self-induced trauma, or from complicating infections. Though cats may experience similar symptoms, they differ from dogs in that a variety of additional primary cutaneous reaction patterns characterize feline allergic skin disease. Commonly reported signs in cats with allergic skin disease include lesions of the eosinophilic granuloma complex, miliary dermatitis, self-induced alopecia and pruritus of the head and neck. Flea, food, and environmental allergies are considered the most common causes of these cutaneous reactions patterns. In cats, fleas are generally agreed to be the most common cause of allergic skin disease[1, 2], though there is controversy in the literature as to the relative frequency of food and environmental allergies. In one study of cats with miliary dermatitis, eosinophilic granulomas or self-induced alopecia, flea, food and environmental allergies were reported in 70%, 17% and 13% of cases respectively[2]. A separate study of 25 cats with similar signs found no evidence of food allergies in any cat, though the use of an over-the-counter, chicken-based diet to perform the diet trials may have affected the results in this case[1]. Further studies are needed to determine the true prevalence of these diseases. Siamese cats have been over-represented in two studies of food allergies in cats and may be predisposed to this disease[3, 4].

Eosinophilic Granuloma Complex: Lesions within the eosinophilic granuloma complex include the indolent ulcer (aka "rodent ulcer"), eosinophilic plaques, and eosinophilic granulomas. Indolent ulcers present as well-circumscribed ulcers, often with a raised border, which occur over the upper lip adjacent to the canines or incisors. The lesions can be either unilateral or bilateral. Eosinophilic plaques are most commonly seen over the ventral abdomen, inguinal region and medial thighs, but can present elsewhere. They are characterized by single or multiple, well-circumscribed, raised, erythematous plaques. The lesions may be exudative and intensely pruritic. Eosinophilic granulomas are raised, yellow to pink cutaneous papules, nodules or plaques. One form of eosinophilic granuloma is the linear granuloma which presents as an elevated linear band of skin down the caudal thigh. Eosinophilic granulomas may also present as swelling of the chin or lips ("fat chin"), within the oral cavity, or on the foot pads, face or abdomen. The lesions can be asymptomatic or pruritic. Eosinophilic granulomas within the oral cavity can lead to discomfort and anorexia.

Miliary Dermatitis: Miliary dermatitis presents as small, multifocal, crusted papules, most commonly distributed along the trunk and neck. The lesions may be difficult to visualize but are readily palpable when running your hand through the coat. The lesions can be mistaken for a bacterial infection but actually represent a primary hypersensitivity reaction. Secondary infections can however occur. Fleas are suggested to be the most common cause of miliary dermatitis.

Self-induced Alopecia: The cat's tongue is much more abrasive than the dog's and is an ideal tool for relieving pruritus. Grooming behavior is also deeply engrained in cats and it is estimated that an indoor cat spends approximately 30% of its waking hours grooming. It is not surprising then that over-grooming is commonly seen with allergic skin disease in cats. The hair-loss which is induced by this behavior is often symmetrical and non-inflammatory, which could lead to suspicions of endocrine alopecia. Cats

may compound this suspicion by performing the over-grooming activity secretly, leading owners to state the hair is falling out, rather than being pulled out. Endocrine alopecia is however a very rare cause of hair-loss in cats, while self-induced alopecia is a very common sign of feline allergic skin disease. It may in fact be the most common sign seen in cats with environmental allergies. In two studies of cats with environmental allergies, self-induced alopecia was the most common sign seen and was present in 41% and 77% of cats[5, 6]. Self-induced alopecia can also be attributed to behavioral causes, though a recent study showed this to be much less common in cats than true pruritus[7]. Feline self-induced is most commonly present along the ventral abdomen but can be present in any area the cat is able to reach.

Pruritus of the Head and Neck: Pruritus of the head and neck may be more commonly observed with food allergies, though all hypersensitivities should be considered. Diseases of the ear, such as mites or polyps should also be investigated. Due to the sharpness of their claws, pruritus of this area can result in severe self trauma in cats.

Treatment: For any hypersensitivity disorder, avoidance of the offending allergen is preferable to long-term medications whenever possible. Eosinophilic granulomas, miliary dermatitis, self-induced alopecia and pruritus of the head and neck are not specific diseases, but merely reaction patterns suggestive of a cutaneous hypersensitivity. A thorough investigation of potential contributing factors should therefore be performed in cats with any of the above signs. Parasitic, bacterial and fungal diseases should be evaluated with skin scrapings, cytology and fungal cultures. Amoxicillin-clavulonate treatment was shown to lead to a significant reduction of eosinophilic plaque size in one study[8], highlighting the importance of bacteria in some cases. Fleas are one of the most commonly implicated triggers of allergic skin disease in cats and their involvement should be ruled out through the stringent use of adulticidal flea preventatives applied to all animals in the household for 1-2 months. One study showed no evidence of fleas or flea dirt on cats which subsequently responded to flea preventatives[1], therefore a lack of these findings should not preclude further work-up for flea allergies. Food allergies should be investigated through the use of either a home cooked, or prescription, novel protein diet, fed exclusively for 8-12 weeks. Cats should be kept indoors throughout a diet trial to prevent hunting. Environmental allergies should only be diagnosed once all other causes have been ruled out. Allergy testing in cats, as in dogs, is unreliable to make a diagnosis of environmental allergies and is instead used primarily to aid in formulating an immunotherapy vaccine for a patient in whom a diagnosis by exclusion has already been made. A recent study showed no difference between normal and atopic cats in the proportion of cats that tested positive with serum allergy testing[6]. Despite difficulties with allergy testing in cats, the response to immunotherapy injections can be acceptable. Double-blinded placebo controlled studies are unavailable but open studies show efficacy rates between 45-100% with immunotherapy injections in cats[9]. In some cats a trigger for the hypersensitivity reaction cannot be determined and a genetic predisposition has been suggested[10]. In these cases, and in atopic cats for which immunotherapy injections are not possible, alternate antipruritic medications are necessary. Antihistamines may be effective in some cases. Cetirizine at a dose of 5 mg/cat, once daily was shown to achieve plasma levels equivalent to those deemed effective in humans[11], though studies on the actual clinical efficacy are lacking. Chlorpheniramine is a popular choice amongst dermatologists and is dosed at 2-4 mg/cat, twice daily. Glucocorticoids may be needed in the initial phases of treatment, regardless of the underlying cause, to palliate intense pruritus and bring lesions under control. Alternatives should be sought if long-term treatment is necessary. Cyclosporine has been shown to be effective for the management of feline atopy. A dose of 25 mg/cat resulted in a good to excellent response after one month in 40% of pruritic cats, 57% of cats with self-induced alopecia and 50% of cats with lesions of the eosinophilic granuloma complex[12]. A second study using higher cyclosporine doses and a treatment duration of at least 3 months showed complete remission of signs in all cats with either pruritus or lesions of the eosinophilic granuloma complex[13].

STAPHYLOCOCCUS AND MALASSEZIA

Staphylococcal skin infections are a very common occurrence in canine dermatology but are less frequently seen with cats. One reason for this may be the reduced ability of staphylococcal organisms to adhere to feline corneocytes relative to people and dogs[14]. The most common isolate obtained from canine skin is *Staphylococcus intermedius* however the predominant isolate from feline skin is less clear. In a recent feline study *S. aureus* and *S. intermedius* were isolated with similar frequency. This was true in cats with normal skin, and in cats with inflammatory skin diseases[15]. While feline staphylococcal skin infections may occur less commonly, they should not be ignored and skin cytology remains an important part of the work-up in feline dermatology.

Malassezia overgrowth is seen very commonly a secondary complication of allergies and other common dermatoses in dogs. *Malassezia* species have been associated with otitis in cats, with a significantly greater frequency of isolation *Malassezia* seen in affected vs. normal cat ears[16, 17], but it has been suggested that they are an otherwise rare component of feline dermatitis[18, 19]. A retrospective evaluation of feline skin biopsies found *Malassezia* organisms in only 2.7% of cats, most frequently in association with serious underlying diseases such as paraneoplastic disease, thymoma-associated exfoliative dermatitis and erythema multiforme[19]. *Malassezia* spp. have also been seen in association with FIV or FeLV infections[20] leading to a suspicion that *Malassezia*-associated dermatitis in cats carries a poor prognosis due to the association with severe systemic disease. While this may be true, and *Malassezia*-associated dermatitis in a cat should raise the clinician's index of suspicion for underlying systemic disease, skin biopsy findings may not accurately reflect the results of in-house cytology, which is more sensitive at detecting surface dwelling *Malassezia* organisms that can be lost during biopsy processing. *Malassezia* spp. can be present in cats with less severe diseases, that are in turn less prone to being biopsied. Though it is uncommon, *Malassezia* spp. have been seen in association with feline allergic skin disease, analogous to the situation with dogs[21]. Hyperpigmentation and lichenification, which occur in dogs with *Malassezia*-associated dermatitis, were not noted. Instead the most suggestive clinical signs in these cats were ventrally distributed, tightly adherent, brownish-scale[21]. Differences between breeds of cats have also recently been elucidated. Devon Rex cats and Sphynx cats were both shown to harbor greater numbers of *Malassezia* organisms than DSHs[22, 23]. A seborrheic dermatitis has also been seen in these breeds, characterized predominantly by seborrhea oleosa of the axilla and groin with alopecia and either hyperpigmentation or reddish-brown surface discoloration[22, 23]. The ventral interdigital spaces and nails folds may also be affected[22, 23]. Greater numbers of *Malassezia* organisms are found on seborrheic Devon Rex cats or Sphynx cats than on their unaffected counterparts[22, 23]. In the Devon Rex cat, this seborrheic-dermatitis was shown to respond to itraconazole, with a corresponding decrease in yeast numbers, supporting the hypothesis that *Malassezia* organisms contribute to the seborrheic condition of these cats[24].

DEMODEX

Three different species of demodex mites have been identified in cats; *D. cati, D. gatoi* and an as yet unnamed species about which little is known. *D. cati* infestations in cats behave similarly to *D. canis* infestations in dogs. *D. cati* is a long, slender-bodied mite which resides in the hair follicles and sebaceous glands and is considered part of the normal feline cutaneous flora. An overgrowth of *D. cati* mites is usually associated with an immunosuppressive condition or treatment such as diabetes, retroviral infections, neoplasia or glucocorticoid administration[25]. Lesions are often localized, consisting of alopecia, follicular plugging, papules, pustules and scaling over the face or legs. Cerumenous otitis may also be present[25]. As yet, a genetic predisposition to *D. cati* infestations, as is seen with *D. canis* in dogs, has not been shown for cats.

D. gatoi infestations are unique among domestic mammals in that they are the only demodex species for which horizontal transmission through casual contact has been reported[15]. *D. gatoi* is a short-bodied mite which lives on the surface on feline skin. There is regional variation in the incidence of this parasite with the highest incidence in North America being in the southern US, particularly in the Gulf Coast region[25]. In fact a recent study from the Gulf Coast region of the US found that 40% of cats which presented for signs of excessive grooming and alopecia were suspected of having *D. gatoi* infections based on

identification of the mite or a positive response to empirical treatment[26]. *D. gatoi* has only recently been described compared to *D. cati* and there is a suspicion that it may represent a commensal of some other species which has only recently been introduced to cats[27]. Hypersensitivity is suspected to be involved in the pathogenesis and marked pruritus can be present in affected cats. It can be difficult to locate mites in such cats presumably due to removal during over-grooming. Conversely, cats can also carry large mite burdens with no clinical signs[27]. The diagnosis is definitively confirmed by skin scrapings, but a response to empirical treatment may be necessary in suspected cases with negative skin scrapings. An ideal treatment regimen has not been determined. The current recommendation is to treat all in-contact cats with a 2% lime sulfur solution, weekly for 6 weeks, though some failures have been seen[27]. Affected cats should start to respond within 3-4 weeks. Alternate effective treatments have included weekly 0.0125% amitraz dips for 12 weeks, and 300 mcg/kg of ivermectin q 24-48 hours for 10 weeks[27]. Selamectin seems to have poor efficacy, even with increased frequency of application[27].

PLASMACELL PODODERMATITIS

Plasmacell pododermatitis is a rare disease of the paw pads in cats. There are no case reports of this disease affecting dogs in the literature, though it has been anecdotally reported by some authors[28]. The disease presents as soft, spongy swelling of the paw pads and may be asymptomatic, though ulceration and lameness can occur. Attempts to find an infectious etiology have been unsuccessful and an immune-mediated pathogenesis is suspected[29]. Hypergammaglobulinemia is frequently seen in association with the disease[30]. Treatment with doxycycline has been shown to be effective in greater than 50% of cases[30]. For those cases non-responsive to doxycycline, glucocorticoids are usually effective.

HERPESVIRAL DERMATITIS

Feline herpesvirus-1 is an uncommon cause of dermatitis in cats. The signs are most often seen on the haired skin of the face and nasal planum and are characterized by ulceration, erosion and crusting. Signs may be seen either with or without concurrent ocular or upper-respiratory disease. Biopsies are required to obtain a diagnosis and reveal necrotizing and ulcerative, predominantly eosinophilic dermatitis. The presence of intranuclear viral inclusions are required for a definitive diagnosis, however these can be difficult to identify, in some cases leading to an incorrect diagnosis of an eosinophilic granuloma or plaque[31]. PCR testing for FHV-1 has a sensitivity of 100% and a specificity of 95%[31] and can lead to increased rates of detection. PCR was positive in 16% of cases previously diagnosed as eosinophilic granulomas in one study[32]. L-lysine, interferon-α, feline interferon-ω, and famciclovir have all been attempted for treatment[33].

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NOTES

CUTANEOUS VASCULITIS
WHAT IS IT AND HOW DO YOU TREAT IT?

Bloom PB [1, 2]
[1] Allergy, Skin and Ear Clinic for Pets, Livonia, MI
[2] Department of Small Animal Clinical Sciences, Dept of Dermatology, Michigan State University

BACKGROUND/ETIOLOGY/PATHOPHYSIOLOGY

Vasculitis is characterized by an aberrant immune response directed toward blood vessels. Histologically there is an inflammatory response INVOLVING and destroying blood vessels leading to ischemic changes (see histopathologic). A vasculopathy is a disease process in which tissue changes are consistent with ischemia but histologically vasculitis can't be identified. Clinically, vasculitis can involve just the skin or there can be systemic involvement (eg uveitis, glomerulonephritis) or both. Vasculitis may be caused by drugs (including vaccinations); insect bites (type I hypersensitivity); bacterial, viral, fungal or rickettsial infections (either induced by direct invasion of the vessel walls by the pathogen or as a result of immune complex formation (most commonly type III hypersensitivity, occasionally type II); genetic (Jack Russell dogs); idiopathic, neoplasia; cutaneous adverse food reactions or an autoimmune disease (systemic lupus erythematosus)[1]

The pathophysiology of vasculitis remains poorly understood, however, immunologic mechanisms appear to play an active role. It has been hypothesized that cytokine-mediated changes in the expression and function of adhesion molecules together with inappropriate activation of leukocytes and endothelial cells are key factors influencing vessel inflammation and damage. Although the primary events that initiate this process remain largely unknown, recent advances in human medicine have allowed investigators to examine the pathogenesis involved in disease. Three of the more popular theories[2] are:

1. Direct binding of antibody to vessel wall antigen (type II hypersensitivity)
2. Circulating immune complex formation and deposition in the vessel wall (type III hypersensitivity);
3. Formation of auto- antibodies (antineutrophil cytoplasmic antibodies (ANCA) – type II hypersensitivity)

Cutaneous small vessel vasculitis (CSVV) affects small dermal vessels especially the post capillary venules. CSVV is the most common form of canine cutaneous vasculitis. In dogs, the cellular infiltrate is the most common method used for categorizing the vasculitis. These forms include neutrophilic leukocytoclastic, neutrophilic non-leukocytoclastic, lymphocytic, eosinophilic or granulomatous. It is important to realize that the findings on biopsy are time dependent. The predominant cell type found on biopsy may only be a reflection of the stage of the disease process rather than a reflection of different diseases. In cutaneous small vessel leukocytoclastic vasculitis, if the lesions are biopsied early (< 24 hours) in the disease process, a granulocytic infiltrate may be seen, while if biopsied 48 hours or later it will be mostly a lymphocytic infiltrate. There are some forms CSVV that are lymphocytic from the onset (eg vaccine associated) [3, 4]

Presentations

Clinical findings that are seen with CSVV include: scaling, alopecia, purpura (bleeding into the skin manifested as petechiation and/or ecchymoses), ulcers, wheals, nodules, dependent pitting edema, acrocyanosis, and panniculitis (if deeper vessels are involved). Distribution of the lesions most commonly involves the distal extremities (including the tip of the ears and tail) and pressure points but may become more diffuse/generalized. Systemic disease may be present as a consequence of the vasculitis (hepatopathies, glomerulonephritis, synovitis-arthritis, gastroenteritis, pleuritis/pericarditis) and/or due to the underlying disease (eg anemia and/or thrombocytopenia with or without systemic lupus erythematosus).

There are a number of subtypes of vasculitis/vasculopathy including

1. Urticarial vasculitis that represents a peculiar subset of small vessel vasculitis. The clinical presentation is that of wheals or serpentine papules, sometimes with surrounding or geographically separate angioedema. In contrast to other forms of urticaria, urticarial vasculitis lesions are slow to

resolve, often lasting for several days and purpura may be present. This form has been reported to be frequently associated with cutaneous adverse food reaction.

2. Proliferative thrombovascular necrosis of the pinna has an unknown etiology. There is no predilection based on signalment. The lesions begin on the pinnal tip and spread proximally on the concave surface. There is a wedged shaped appearance to the lesion – with the tip of the wedge most proximally. There are ulcers, crusts and scales present.
3. Familial (autosomal recessive) cutaneous vasculopathy in German Shepherd dogs has been reported in Canada. This genodermatosis is frequently triggered by vaccinations; with the lesions appearing 7-10 days post vaccination. The puppy is systemically ill. Clinical signs, first noted at 4-6 weeks of age include (lethargy, lameness, joint swelling, and pyrexia +/- lymphadenopathy). Cutaneous lesions include firm swelling of the bridge of the nose, ulcers and crusting on the pinnae, nasal planum and the tip of the tail. Footpads are swollen, depigmented and may ulcerate. CBC, serum chemistry profiles, ANA titers, RF titers, Coombs tests and immunoglobulin levels have all been normal
4. Proliferative arteritis of the nasal planum has been reported in Saint Bernards and Giant Schnauzers.[5] The speaker has also identified it in a Great Dane. The etiology is unknown. There are linear ulcers on the nasal planum (nasal philtrum) that are non-pruritic. There may be significant hemorrhage from the lesions. Therapy with prednisone, topical steroids, tetracycline, niacinamide, calcineurin inhibitors and fatty acids (omega 3/6 combination) have all been reported to be effective in managing this disease.
5. Idiopathic cutaneous and renal glomerular vasculopathy in racing Greyhounds ("Alabama rot"). Despite its name it has been reported in other breeds (Great Dane).[6] There is no age or sex predilection. There may be a genetic predisposition to this disease. Clinically it begins as multifocal erythematous cutaneous swellings that then ulcerate. The lesions involve the limbs +/- abdomen and trunk. The swellings may drain a serosanguineous fluid. Pitting edema may be present. Systemic signs (fever, lethargy, GI signs) including signs associated with acute renal failure have been reported. Etiology is thought to be associated with verotoxin produced by *E. coli* that is present in undercooked beef products. A verotoxin is an exotoxin produced by *E. coli* version and is named because of the ability of the toxic protein to kill Vero cells (African green monkey kidney cells) in culture.
6. Vasculitis of Scottish terrier has been reported as a probable genodermatosis. At 3-4 weeks of age the dogs developed a nasal discharge with subsequent ulceration and destruction of the nasal planum and nostrils. There is no effective treatment.
7. Vasculitis of Jack Russell Terriers has been reported. In one case report the age of affected dogs (5) ranged from 3 months old to 11 years of age. The cause of the disease is not known but in 3 of 5 dogs the symptoms occurred at 2-3 weeks post vaccination. The author suggests that perhaps these dogs had adult onset dermatomyositis. There is a good possibility that these dogs had vasculitis.
8. Cold Agglutinin Disease (CAD) is a rare cause of vasculitis in dogs and cats. Exposure to cold is typically a relevant factor in the history. CAD may be idiopathic or a secondary disease (eg lead poisoning) so a search for an underlying cause is essential. A Coombs test should be positive at 4^{O} C and negative test at 37^{O} C.
9. Ischemic dermatopathy
    a. **Dermatomyositis occurs as a genodermatosis in collies and shelties.[7] It may** occur spontaneously in adults of other breeds (not inherited form). In collies and shelties the age of onset is between 6 weeks and 1 year of age, most commonly they are less than 6 months of age. The lesions may be fairly limited and heal as the puppy matures or they may progress. Usually the lesions stabilize by the time the dog is a year old. The cutaneous lesions, which are usually the more prominent clinical sign, include alopecia, scaling, crusts, erosions, ulcers, depigmentation, hyperpigmentation and scarring. These lesions occur on the face, mucocutaneous junctions, carpal and tarsal regions and the tip of the tail, the pinna and elbows. Onychodystrophy may also be present. Secondary bacterial pyodermas may occur. Muscle involvement tends to be proportional to the severity of the skin lesions and is usually identified subsequent to the cutaneous lesions developing. These dogs may develop megaesophagus or muscle atrophy involving the muscles of mastication and ambulation. Differential diagnoses

include demodicosis, dermatophytosis, superficial bacterial folliculitis, discoid lupus erythematosus and epidermolysis bullosa simplex. In the author's experience, puppies are mostly commonly presented with limited facial lesions that the breeder claims are wounds/scars from the other puppies or a cat in the house. Diagnosis is based on signalment, physical examination and histopathologic changes consistent with a vasculopathy.

b. Post injection alopecia is a syndrome that occurs 2-12 months after receiving a vaccination (usually rabies) or after an injection of a long-acting corticosteroids or progestational compound. Small white breeds of dogs seem to be at risk for developing these lesions. SQ or IM injections have no impact on the occurrence of this reaction. Lesions consist of scaling, alopecia, plaques, hyper-pigmentation, nodules, erosions, crusts and cutaneous atrophy (scarring). Histologically, in addition to the vasculitis changes, there will be a focal lymphoid nodule present in the lower dermis or panniculus (panniculitis).
    i. Proper history collection is critical since a subset of these dogs develop lesions at sites distant from the injection site and can be improperly diagnosed as the idiopathic form (see below) [8]
c. Idiopathic form occurs in adult dogs of any breed. This may be a localized disease (eg pinna) or generalized. Because ischemia is a consequence of a vasculopathy, all diseases (as previously mentioned) need to be ruled out before a diagnosis of idiopathy is established.

Diagnosis

The diagnosis of any skin disease is based on detailed history taking, clinical findings (identification of primary lesions, distribution of lesions), laboratory testing and therapeutic trials. For vasculitis the most beneficial laboratory procedure is histopathologic evaluation. Evaluation of patients with confirmed vasculitis should include a detailed history of drug exposures (including vaccinations), a thorough examination (including a retinal exam) and as a minimum database – a CBC, serum chemistry profile and urinalysis. If a urine dipstick is positive for protein, a urine total protein/creatinine ratio or a test for microalbuminuria should also be performed. Other diagnostics that may be performed depend on the signalment and presentation. These tests could include; titers for tick borne diseases, testing for *Bartonella*, blood, tissue or urine cultures; Coomb's test (warm and cold), thoracic or abdominal radiographs; or abdominal ultrasound.

Histopathologic

Because there are only a limited number of histopathologic manifestations of vasculitis, regardless of the cause, it is best to think of vasculitis as a reaction pattern with a variety of different etiologies. Regardless of the cause, vasculitis is a disease process characterized histologically by inflammation and destruction of blood vessels and ischemic changes. The vascular changes that may be seen include endothelial cell swelling, neutrophilic invasion of blood vessel walls, the presence of disrupted neutrophils (leukocytoclastic), extravasation of red blood cells, and fibrinoid necrosis of the blood vessels walls, thrombosis of affected vessels, hyalinization and fibrosis of vessel walls. The ischemic changes are characterized by smudging and paleness of the dermal collagen, a cell poor interface dermatitis, dyskeratotic keratinocytes, full thickness necrosis of the epidermis, follicular and adnexal atrophy ("fading follicle").

Differential diagnosis

Coagulopathies, frostbite, DIC, demodicosis, dermatophytosis, superficial bacterial folliculitis and discoid lupus erythematosus are possible differential diagnoses depending on the clinical presentation (signalment, historical information, distribution and appearance of the lesions).

Treatment

The first step is to identify and treat the underlying cause (if possible) and/or avoid it (eg drug induced). When planning treatment be sure to consider the severity of the disease so that the treatment is not worse than the disease. Depending on the severity of the symptoms therapy may include: pentoxifylline, glucocorticoids (GC), other immunosuppressive agents, sulfones and immunomodulating agents. All cases of vasculitis that the author treats systemically will have pentoxifylline included as part (or all) of the initial therapy. Pentoxifylline is a methyl-xanthine derivative that increases RBC deformability and lowers blood viscosity thereby allowing for better blood flow through narrowed/edematous vessels.[9] It also suppresses synthesis of proinflammatory cytokines such as IL-1, IL-4, IL-12 and TNF-α. Pentoxifylline is administered at 15 mg/kg tid. There may be a 30-90 day lag before full clinical response is seen. Vitamin E (400-800 IU bid) and Essential Fatty Acids may also be useful as part of the treatment since these nutrients have anti-inflammatory properties and anti-oxidant activities.

Tetracycline/Niacinamide may be used in milder forms of the disease.[10] Tetracycline and niacinamide have various anti-inflammatory & immunomodulating properties. The dosage for tetracycline and niacinamide in dogs or cats <10 kg is 250 mg of each, q 8 hours. For dogs >10kg - 500 mg of tetracycline and 500 mg of niacinamide q 8 hours are administered. If there is clinical response (usually waiting for a few months) it is slowly decreased from tid, to bid to sid. Side effects are rare but when they occur as usually due to niacinamide. These side effects include vomiting, anorexia, lethargy, diarrhea and elevated liver enzymes. Tetracycline may lower seizure threshold in epileptics and also may cause a hepatopathy.

Glucocorticoids (GC) are the main stay of therapy for many forms of vasculitis. The most potent topical GC (veterinary product) is a product containing fluocinolone acetonide (Synotic). If the disease is localized (eg tip of the pinna) but is not adequately controlled with synotic, the author uses an even more potent product containing desoximetasone – at a concentration of 0.25%. The topical medication is applied bid until clinical remission (not to exceed 21 days) and then tapered slowly over the next few months. Be sure to have the owners wear gloves when applying these products. Please note that topical steroids may cause pu/pd/polyphagia. This sensitivity to steroids is quite variable and may occur in unexpected situations. If side effects occur or if the lesions fail to respond to topical steroids, topical tacrolimus (0.1%) may be helpful.

Prednisone is administered at 1 mg/# bid for 4 days then ½ mg/# bid for another 10 days. The dog is rechecked every 14 days. If the disease is in remission, the dose is decreased 25% every 14 days. The author defines "remission" as the absence of any active lesions. DON'T TAPER THE DOSE TOO QUICKLY. The goal is to maintain the dog on 0.25 mg/# or less every other day. If this is not achievable, then azathioprine is added to the therapy (see below).

If an animal fails to respond to prednisone, not only will other immunosuppressive agents (see below) be added to the therapy but also changing to either dexamethasone or triamcinolone may be necessary. For either of these drugs, use 0.05-0.1 mg/# bid as the starting dose and then taper as previously discussed.

Animals on chronic GC, regardless of dose should have a CBC, serum chemistry profile, urinalysis and urine CULTURE (looking for asymptomatic bacteriuria) every 6 months. The importance of this later recommendation was reported in 2 studies. Both these studies reviewed the incidence of bacterial urinary tract infections in dogs on long term steroid. In one study it occurred in 39% of the dogs and it occurred in 21% of the dogs in the other study[11, 12]. Counter intuitively both studies reported that in their groups of dogs there was no significant differences in the occurrence of the urinary tract infection in regards to the frequency of drug administration (eg alternate-day versus daily), type of glucocorticoid,

dosage (even a low dose) or duration of therapy. In the later study pyuria was not identified in 48% of the samples that yielded growth. Because of this both studies concluded that urine sediment analysis alone was not an adequate means of detecting urinary tract infections in these dogs [11,12] Lastly, in the later study none of the owners reported seeing any clinical signs of UTI. Bottom-line is that depending on clinical signs and/or urinalysis alone will miss UTI in a significant number of dogs

Azathioprine (AZA) is an antimetabolite that is a competitive inhibitor of purine. AZA has a lag phase of one to six weeks before it reaches its full potential. The drug is administered concurrently with GC. The initial dose of azathioprine is 1.0 mg/# sid. Once remission is achieved, and the dog is either off of GC or the lowest dose of GC has been obtained, AZA is then tapered, also every 14-30 days. Usually the author will decrease the frequency, not the dose of azathioprine; first decreasing it to every other day and then if the disease is still in remission, to every 72 hours. A CBC, platelet count, serum chemistry profile are performed every 14 days for 2 months, then q 30 days for 2 months then q 3 months for as long as the dog is on azathioprine. Potential adverse effects include anemia, leukopenia, thrombocytopenia, hypersensitivity reactions (especially of the liver) and/or pancreatitis. AZA should not be used in cats- it may cause irreversible bone marrow suppression.

Chlorambucil (CAL) in dogs who fail to respond to azathioprine or can't tolerate it. The protocol/precautions/monitoring for CAL is the same as with AZA. The induction dose is 0.1-0.2 mg/**KG**/day.

Cyclosporine (CSA) could be added to cases that fail to respond to the previous treatments. Be sure to use modified cyclosporine (Atopica®) since unmodified CSA is not absorbed as well. The dosage is 5 mg/kg sid.

In cases of neutrophilic vasculitis that fail to respond to the above treatment, sulfasalazine (SZA) at a dose of 25 mg/kg tid (maximum 3 grams/day) may be useful. Side effects associated with this drug include anemia, KCS and hepatotoxicity so a CBC, serum chemistry profile and Schirmer tear test are performed every 14 days for 2 months, then q 30 days for 2 months then q 3 months for as long as the dog is on SZA. In cases of neutrophilic vasculitis that fail SZA, they may sometimes be successfully treated with dapsone, however, dapsone appears to be more toxic than SZA especially to the liver.

In cases of eosinophilic vasculitis, urticarial vasculitis or poorly responsive vasculitis, a home cooked elimination diet trial should be performed.

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NOTES

CANINE ACRAL LICK DERMATITIS

John C. Angus, DVM, DACVD
Animal Dermatology Clinic
150 N. San Gabriel Blvd, Suite 400
Pasadena, CA 91001

INTRODUCTION

Acral lick dermatitis (ALD) is among the top 10 most common dermatologic diseases of dogs[1-2]. ALD is frustrating for the veterinarian, expensive for the owners, miserable for the patient, and relapse is common. Therapeutic success rates are low, ranging from 20-65%[2] . In spite of this, there is remarkably little active clinical research to improve veterinary understanding of ALD. Since 1980, only 10 original research articles have been published on canine ALD; most were treatment trials with topical therapy[3], psychotropic drugs[4-7], narcotic antagonists[8-9], and electric shock aversion therapy[10]. Only three reporting histopathologic and microbiologic findings of clinical cases[3,9,11].

CLINICAL PRESENTATION

ALD is a clinical syndrome characterized by self-traumatizing licking resulting in progressive development of well-circumscribed, firm, proliferative, erosive/ulcerative, alopecic plaques or nodules on the lower portion of the limb. While appearance and size of the lesion can be quite variable, the most consistent feature is excessive, persistent licking. Lesions are most commonly found on the dorsal aspect of distal forelimb, occasionally extending down the metacarpus, or up to the elbow. Less commonly the lateral tarsus or metatarsus is involved. A recent survey[11], demonstrated front limb only involvement in 21 of 31 dogs (68%), front and hind limb involvement in an additional 6 of 31 (19%), and hind limb only involvement in only 4 of 31 (13%). Lesions are often painful with patients resisting manipulation or palpation; some dogs demonstrate lameness or decreased activity. Any breed can be affected, but there is a predisposition for large breed dogs with short coats: Doberman Pinscher, Great Dane, Labrador Retriever, Boxer, and Weimaraner[2,11]. Other frequently mentioned breeds are German Shepherd, Golden Retriever, and Irish Setter. Median age of onset is 4 years (range 1 – 12 years)[11].

CAUSE

The etiology of ALD is complex and multifactorial. Similar to the etiologic approach proposed to simplify understanding of chronic otitis, dermatologists approach ALD considering all causes and contributing factors in three categories: (1) predisposing, (2) primary, and (3) perpetuating factors.

Table: Multifactorial causes of canine acral lick granuloma

Predisposing	Primary	Perpetuating
Short Hair Coat	**Food Allergy**	**Deep bacterial infection**
Breed	**Atopic Dermatitis**	Entrapped free hair shafts
	Osteoarthritis	Apocrine Gland inflammation
	Trauma	Fibrosis
	Neoplasia	Reinforced behavior
	Fungal infection	
	Foreign Body	
	Parasthesia / Neuropathy	
	Behavior Disorders	

Predisposing factors are things that do not directly cause ALD but make initiation and progression of ALD more likely. This includes breed predisposition and short hair coat over affected limbs.

Primary causes are conditions that initiate licking at the target site, resulting in development and progression of clinical lesions. Foremost among these are disorders that cause pruritus: food allergy and atopy. Less common causes include trauma, neoplasia, dermatophytosis, foreign body, osteoarthritis, parasthesia, neuropathy, and behavior disorder. A recent case series reported clinical lesions, resulting from a Kirshner pin, lymphoma, mast cell tumor, sporotrichosis and Leishmania[12].

ALD is often described as a "behavioral" or "psychogenic" dermatosis[3, 13-15]. However, in our clinic, primary behavior cause is rare; food allergy is the most common, followed by atopy. In cases with primary behavior disorder and no other identifiable cause, patients typically exhibited multiple behavioral problems; including, separation anxiety, phobia, or other stereotypic behaviors, such as tail-chasing, circling, wool sucking, fly biting, or rhythmic barking. If a dog with ALD presents with additional behavior problems, then move primary behavior cause higher on the list of differential diagnoses; however, in the absence of concurrent behavioral disorders, pursue food allergy, atopy, and other diseases first, then address behavior as a perpetuating factor (see below).

Our understanding the primary causes of ALD would benefit from collaborative prospective studies with both dermatology and behavioral specialties to better determine etiology and characteristics of primary behavioral ALD vs primary allergic ALD. A good model for such research is a recent study of another "behavioral" dermatosis, feline psychogenic alopecia[16]. This study evaluated 21 adult cats with a diagnosis of psychogenic alopecia; in 19 cats a primary pruritic disease was identified. Only 2 cats found to have a psychogenic cause. Food allergy was the most common cause, confirmed in 12 of 21 cats.

Perpetuating factors to consider in dogs with ALD are conditions that result in an amplifying cycle of self-traumatic licking. The most common perpetuating factors are (1) deep bacterial infection, (2) ruptured hair follicules and free keratin debris, (3) hidradenitis, and (4) reinforcing behavior changes
.
In a recent prospective study[11], deep tissue bacterial infection was identified in 29 of 31 dogs (94%). One dog was culture positive for *Microsporum gypseum*. The most common deep tissue isolates were *Staphylococcus* (58%), *Pseudomonas* (8%), and *Enterobacter* (8%). Antibiotic susceptibility profiles were unpredictable; 52% of isolates were resistant to three or more antibiotic drug classes commonly used for Staphylococcal pyoderma (cephalosporin, clindamycin, potentiated sulfonamides, amoxicillin-clavulanate, and fluoroquinolones). Methicillin-resistant *Staphylococcus* was isolated in 25% of cases. Culture obtained from surface swab was a poor predictor of deep isolates; therefore antibiotic selection should be based on culture obtained by biopsy or by squeezing up deep purulent exudates.

Another major cause for progression and perpetuation of ALD is ruptured hair follicles and inflammatory response to keratin in the free hair shafts. Dogs start licking as a manifestation of pruritus, which may result in focal bacterial folliculitis, which is pruritic and stimulates more licking. In short-coated breeds, licking results in rupture of hair follicles and forcing of short, stiff hairs into the deep dermis. Keratin is phenomenally irritating to tissues and elicits a profound acute and chronic inflammation. Hair shaft foreign bodies are very painful. This combination of pruritus and pain results in amplification of the desire to lick at the region. Over time, these changes progress to commonly described histopathologic features of ALD: ulceration, dermal fibrosis with a vertical streaking pattern, thickened and elongated hair follicles, free hair shafts, and diffuse pyogranulomatous to lymphocytic-plasmocytic inflammation In the prospective study of 31 dogs[11], epitrichial sweat glands were also found to be heavily involved, exhibiting periglandular inflammation (90%), hypertrophy (81%), inspissation (81%), dilation (71%), severe focal inflammation in the glands (hidradenitis; 29%) and glandular rupture with secretions free in the tissue (10%).

Behavior is more likely involved in progression and perpetuation of canine ALD rather than as a primary cause. Repetitive, "compulsive" licking in ALD has been compared to obsessive-compulsive disorder (OCD) in humans[5-7]. Unfortunately very little is known about neurophysiology and neurochemistry of dogs with ALD to compare with the neurophysiology of humans with OCD, which has been studied extensively. An interesting finding in human patients with OCD is an abnormal neural pathway between

the frontal lobes (consciousness and perception) and the caudate lobe of the basal ganglia (planning and execution of movements). As a result OCD patients demonstrate debilitating impulsive repetitive behaviors, hand-washing, checking of lights, stoves, door locks, unplugged irons; the patient is consciously aware they just washed their hands, but the information that the action is completed and no longer needs to be done does not get processed properly and the patient repeats the behavior. I doubt very much that dogs are having intrusive thoughts and planning-completion abnormalities such as "I should lick my paw…I just licked my paw…my paw needs licking?"

The only evidence for comparison of ALD in dogs and OCD in humans, relates to observation of beneficial response to Selective Serotonin Reuptake Inhibitors in both groups. Serotonin is a vital neuromodulator involved in nearly every aspect of normal behaviors, responses, and actions. Repetitive motor activities in OCD patients increase serotonin activity, creating a self-medicating feedback loop that reinforces the behavior. However, OCD is not the only disorder with response to SSRI and many repetitive stereotypic behaviors unrelated to OCD are characterized by self-reinforcing serotonin pathways. Dogs with ALD may also experience a similar self-reinforcing feedback, where licking provides both a temporary alteration of local sensation (relief of pain/pruritus) and pleasurable increase in serotonin activity; perhaps SSRI therapy helps modulate self-reinforcing behavior rather than overcoming a primary neurophysiologic disorder as described by the OCD model.

DIAGNOSIS

Diagnosis should focus on both primary cause and perpetuating factors. Use both dermatology and behavior history questionnaires to assist in early identification allergic or behavior disorders. Any pruritus or otitis? Think allergy; however, do not rule out allergy if ALD is the only manifestation of pruritus. If behavioral history shows concurrent anxiety, phobia, or stereotypic behaviors, then more aggressive pursuit of behavior is warranted. In most cases, think food or atopy with infection first.

The initial minimum database should include, cytology, skin scrape for demodicosis, and dermatophyte culture. Documentation of the size and appearance of the lesion with digital photography, calipers, or tracing of the lesion through clear acetate is important for later comparison.

Biopsy for histopathologic confirmation and bacterial culture and sensitivity is also recommended in rapidly developing or unusual appearing lesions. Histopathology is the most direct method for ruling out organic causes that mimic allergic ALD such as neoplasia or deep mycosis. Of greater value in allergic ALD is deep tissue culture and sensitivity. 95% of dogs with ALD have deep pyoderma, and most have bacteria with unpredictable susceptibility to antibiotics. Because ALD may require prolonged treatment (2-6 months), antibiotic selection based on culture increases the opportunity for successful therapy. Surface swabs are not sufficient, since they are more likely to identify oral contaminants or more routine surface bacteria rather than the bacteria present deeper in the tissue. If a biopsy is not appropriate or feasible for the patient, a quality sample for culture can be obtained by squeezing the lesion until a small quantity of deep exudate emerges from a follicular pore.

Elimination diet trial is an essential test for canine ALD. Following 8-12 week trial, ask – is the dog licking less and is the lesion smaller. The answer may be yes because of resolution of infection; therefore the true diagnostic test is provocative challenge with the original diet. Intradermal allergy testing or allergy serology to identify allergens for inclusion in allergen specific immunotherapy is indicated in any patient that fails to respond to elimination diet trial. Radiography of the affected limb may be helpful to evaluate for underlying osteoarthritis, implants, neoplasia, or deep mycotic infection. In chronic ALD, the presence of periosteal reaction on radiograph is a negative prognostic factor.

TREATMENT

Focus on three components: (1) Management of primary disease, (2) Effective antibiotic therapy for deep pyoderma, and (3) prevention of ongoing licking; failure in any one of these areas will likely result in poor response, recurrence, or progression. Treatment of primary allergic disease may include diet, allergen immunotherapy, cyclosporine (Atopica, Novartis), and short courses of steroids to reduce

pruritus. Use corticosteroid doses and protocols employed for routine atopic dermatitis; avoid higher, longer, or aggressive steroid usage simply because ALD is a more severe than other pruritic disease. Intralesional steroids may actually prolong infection and ALD.

Managing the deep bacterial infection requires a safe, effective, and convenient antibiotic that the owners and the animal can tolerate for a protracted periods. Because resistant bacteria are common, and because the owner will be administering oral antibiotics for prolonged courses, try to choose an effective antibiotic based on susceptibility profile that is administered easily, on a simple schedule. cefpodoxime or ormethoprim sulfadimethoxine one time daily is ideal for susceptible bacteria. Fluoroquinolones can be used for gram-negative infections where no other oral choice is rationale. Use the highest achievable dose or combining with a second antibiotic to minimize risk of developing resistant strains. Other choices based on culture can include cephalexin, clindamycin, chloramphenicol, doxycycline, and amoxicillin-clavulanate. Always aim high with dose and duration, as relapse and failure are common.

Topical mupirocin ointment is excellent for *Staphylococcus*, including methicillin-resistant strains. Topical benzoyl peroxide gels and washes can be beneficial as an antiseptic, to open hair follicles and facilitate removal of keratin debris. Epsom salt soaks and massaging hydrotherapy may help. Other topical therapies with variable utility and efficacy include, fluocinolone and DMSO, flunixin meglamine, and capsaicin. A mixture of 1/3 liquid HEET and 2/3 Bitter Apple has also been described. Use caution with any topical therapy if therapy directs the dog's attention to the area, causing increased licking rather than less. Ideally actively distract the dog by taking for a walk after application of topical therapy.

Pain from entrapped hair shafts and deep pyoderma can be a major factor that stimulates continued "compulsive" licking. Pain may be an even more important factor than pruritus in the perpetuation of ALD. Adjunctive therapy with analgesics such as non-steroidal anti-inflammatory drugs, gabapentin and/or amantadine may be useful, but has not been thoroughly researched. Gabapentin is an antiepileptic drug with utility in managing neuropathic pain. Amantadine is an NMDA receptor antagonist. Check with your local veterinary anesthesiologist for guidance if you do not have experience with these drugs.

Other treatments including surgery, cryotherapy, laser ablation, radiation therapy, and acupuncture have been reported with variable success. I prefer to use laser ablation only after the primary disease is diagnosed and managed and antibiotics have been administered to maximal benefit. Patience is necessary; the remaining lesion is smaller, and contains only fibrosis, trapped hair shafts, and foci of bacteria. Manage as any open wound healing by second intention; prevent continued licking.

Behavioral therapy is focused on two areas – behavior modification and drugs. Seek expert advice for effective protocols for concurrent behavioral diagnosis (separation anxiety, phobia, or stereotypic behaviors). Behavior modification therapy may include avoidance of recognized triggers, counter-conditioning, and distraction techniques, such as social and environmental stimulation, exercise, and increased play. Aversion therapy with shock collars has also been evaluated[10]. However, caution and guidance from an experienced behaviorist is strongly recommended before using this therapy. Aversion is one of the hardest behavior modification techniques to apply effectively; 100% application of the stimulus is required. Partial or intermittent application can actually reinforce the behavior rather than extinguishing it. Also aversive stimuli does very little to resolve pain associated with impacted hair shafts, ruptured sweat glands, and deep pyoderma.
Drug therapy may help resolve perpetuating, self-medicating serotonin feedback loop; consider tricyclic antidepressant: clomipramine and Selective Serotonin Reuptake Inhibitor: fluoxetine hydrochloride.

Bandaging, using E-collars, muzzles, and other techniques to physically restrain the dog and preventing licking meets with mixed results. Early on, restraint may actually be counterproductive, as pain and pruritus are usually very high and the motivation to lick is powerful. Some dogs will resort to self-destructive licking around the restrains or at other limbs, resulting in worse disease not better. I prefer to wait until the lesion is improving and stimulus is reduced before attempting restraint. I will definitely use restraint following laser ablation or other surgical intervention.

SUMMARY

- ALD is a multifactorial disease with predisposing, primary, and perpetuating factors
- Think of atopy and food allergy and secondary deep pyoderma first.
- 95% of acral lick lesions have deep bacterial infections
- Antimicrobial susceptibility is less predictable than routine pyoderma
- Culture by biopsy or by squeezing up deep exudates
- Treat with antibiotics 2 weeks beyond clinical resolution
- Food trials are an essential diagnostic test for every patient
- Think about effective analgesia therapy rather corticosteroids
- Most dogs with primary behavior ALD exhibit other behavior problems

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NOTES

SELF TRAUMATIZING CATS

Waisglass, SE
North Toronto Animal Clinic, Dermatology and Behavior Specialists, Thornhill, Ontario, Canada
Veterinary Emergency Clinic and Referral Hospital of Toronto, Ontario, Canada
Adjunct Professor, Ontario Veterinary College, Guelph, Ontario, Canada

THE CONNECTION BETWEEN THE BRAIN AND THE SKIN

Behavior and medicine (or physiology) are not mutually exclusive; there is a complex interaction between the two. Studies published recently in the British Journal of Dermatology concluded that human patients subjected to brief psychological stress (PS) developed an increase in Psoriasis Area and Severity Index (PASI) and itch 4 weeks later.[1] There was a significant psychological-stress induced increase in cytotoxic CD8+ T lymphocytes in patients with psoriasis when compared to healthy volunteers.[2] Psychological stress decreases epidermal proliferation and differentiation. It impairs epidermal permeability barrier homeostasis, and decreases stratum corneum return to integrity, as measured by trans epidermal water loss (TEWL), in much the same way as exogenous glucocorticoids.[3-4] Many of the adverse effects of PS on epidermal structure and function have been attributed to increased endogenous glucocorticoids, and approaches that are designed to reduce either the glucocorticoid production or action might benefit cutaneous disorders that are provoked or exacerbated by PS.[5]

In mice, stress induces nerve growth factor and substance P-dependent neurogenic inflammation. Sound stress induced dendritic cell (DC) maturation and up-regulated intercellular adhesion molecule-1 (ICAM-1) expression. Blocking of ICAM-1/leukocyte function-associated antigen-1 interactions significantly abrogated the stress-induced numeric increase, maturation, and migration of dermal DCs *in vivo* and also reduced stress induced keratinocyte apoptosis and endothelial cell expression of ICAM-1.[6]

Alopecia in cats may be a result of an array of medical disorders. Medical problems can turn into behavioral conditions; regardless of the underlying cause, self-induced alopecia may progress to a compulsive disorder in cats.[7-8] On the other hand, feline self-trauma leading to hair loss may be a consequence of displacement behavior that may arise from environmental and social stressors or situations causing conflict, frustration, or anxiety.[7] It is easy to find some environmental stressor that could serve as the "trigger" that initiated a behavior in virtually any patient, but the mere presence of an event does not make for a diagnosis.

Behavior and medical diseases may have different underlying etiologies and yet coexist; there is no rule that an individual with a compulsive disorder can't also suffer from environmental allergies.

And so the challenge is in deciding whether any skin condition is medical leading to behavioral, behavioral leading to medical, primarily behavioral or primarily medical. The diagnosis in the feline patient that is self-traumatizing can therefore be a daunting task.

FELINE ALOPECIA – IS IT ON THEIR SKIN OR IN THEIR HEAD?

THE MEDICAL APPROACH

A comprehensive medical approach is required to make a definitive diagnosis before diagnosing virtually any behavioral condition. Cost concerns (especially in the current economic environment) and owner compliance may limit testing in some instances so that a presumptive, rather than a definitive, diagnosis is made. While this is especially true for the family veterinarian, referral practitioners can also fall into the trap of leaping to a diagnosis. Because of this, veterinarians may accidentally misdiagnose some cats as having a behavioral etiology, when in fact there is a medical cause.

THE STUDY

Psychogenic alopecia is a diagnosis of exclusion. A clinical trial was performed in our dermatology and behavior referral practice on cats that were suspected of having psychogenic alopecia by their family veterinarian.[9] Although the incidence of psychogenic alopecia in cats is unknown, we hypothesized that the condition is over-diagnosed.

Cats were only entered into the trial if there was hair loss in the absence of any primary lesions (other than self-excoriation), if the problem was continually present for at least 6 months, and if there was no obvious evidence of parasites. Cats with head and neck lesions were excluded due to the high prevalence of adverse food reactions in these patients.[10] Each cat was first assessed by a veterinary behaviorist (GML), to determine whether the pet had behaviors that were consistent with psychogenic alopecia. Then the cats were transferred to the author for dermatological evaluation. Each cat was first examined and photographed and anal sacs were expressed (not the most fun part of the study!). For each cat, a trichogram, CBC, biochemical profile with thyroid, FELV/FIV testing, urinalysis, fungal culture and skin scraping were performed. Skin biopsy specimens were collected and submitted (blindly – i.e. without history) to a dermatohistopathologist. If there were no abnormal findings at the first visit, each cat was treated with selamectin (Revolution™) and a food trial of minimum 8 weeks duration was performed (Hills prescription diet Z/D low allergen™). If the cat improved significantly, it was challenged with its regular food. If there was no or partial improvement, the cat was then treated with steroids (a "steroid response trial") to rule out an unidentified pruritus (such as environmental hypersensitivity). We chose up to 2 injections of Depomedrol to ensure client (and patient) compliance. Allergy tests were not performed as the goal of the study was to determine whether the cats were self-traumatizing due to pruritus; a positive allergy test does not prove that the self-trauma is a result of allergies.

One might wonder about a potential "calming" effect of steroids on behavior? We considered this possibility but were unable to find good documentation to support this contention. Indeed, a recent study looked at the effects of corticosteroids in dogs. Dogs that were treated with either methylprednisolone, prednisolone, or dexamethasone were reported to have nervousness, restlessness, an increase in startle responses, food guarding, decreased activity, irritation related aggression, increased avoidance response and increased barking.[11] Steroids would be unlikely to ameliorate an anxiety or compulsive disorder. Indeed, one might expect that if steroids affected compulsive or anxiety related disorders in people, psychiatrists would be treating their patients with steroids rather than anti-obsessional or anxiolytic drugs.

Using this protocol, of 21 cases, 16 (76.2%) had a medical etiology, 2 (9.5%) were psychogenic alopecia and 3 (14.3%) were combined medical and behavioral. If we assume that the steroid responsive patients were environmentally allergic, then of the medical problems, a combination of environment and adverse food reactions were most common, followed by adverse food reactions alone, environment alone, and parasitic hypersensitivity.

IN THEIR SKIN

Specifically, medical conditions identified in these cats were concurrent adverse food reaction plus environmental hypersensitivity (5), adverse food reaction (4), hypersensitivity of undetermined cause (2), concurrent adverse food reaction, environmental hypersensitivity and flea allergy dermatitis (1), environmental hypersensitivity alone (1), parasitic dermatosis (i.e., clinical response to parasiticide administration (1), parasitic dermatosis and bacterial dermatitis (1), and parasitic dermatosis and hyperthyroidism (1). Fifty-two percent of the patients had more than one factor that was contributing to the self trauma. Skin biopsy specimens were obtained from 20 of the 21 cats, and 14 of the 20 (70%) had inflammatory skin lesions. There was no indication in any of the specimens of an endocrinopathy. All cats with histological evidence of inflammation had a medical condition associated with pruritus. No histological abnormalities were seen in skin biopsy specimens from 6 cats. Of these cats, 2 had a compulsive disorder and 4 had an adverse food reaction, environmental hypersensitivity, or both. Therefore, while biopsy results were helpful (in that an inflammatory response was found in most medical cases), there were a number of cats with histologically normal skin that also had a medical cause.

IN THEIR HEAD?

A diagnosis of psychogenic alopecia should made only if primary dermatologic and other medical conditions have first been thoroughly ruled out.[12] Hair loss was determined to be entirely psychogenic in only 2 of the 21 cats in our study. These were considered to be a result of a compulsive disorder whereby behaviors are exhibited independent of the original context and have no apparent goal.[7-8] They can be repetitive, exaggerated, sustained, or so intense that they might be difficult to interrupt. The rationale for identifying these behaviors as compulsive or obsessive-compulsive is that they resemble compulsive disorders identified in humans such as repetitive hand washing, in regard to clinical appearance and response to neuropharmacologic agents. Although the pathophysiology of compulsive disorders is not entirely understood, an underlying alteration in neurotransmitters is a likely factor, and pharmacologic intervention is often needed. Alterations in β-endorphins, dopamine, and serotonin have all been implicated in compulsive disorders, primarily on the basis of response to treatment, but abnormal serotonin metabolism has been suggested to be the primary mechanism by which these disorders are induced.[7] In fact, drugs that inhibit serotonin reuptake (e.g., clomipramine and fluoxetine) have been shown to be most effective in the treatment of cats and dogs with compulsive disorders, and direct evidence of serotonin involvement has been identified. [7-8, 13-16] Trichotillomania in humans is an impulse control disorder and could be an alternative explanation for these behaviors in pets.[17]

IN THEIR HEAD AND IN THEIR SKIN

In 3 of the 21 cats, a behavioral component was identified in addition to a medical condition (environmental hypersensitivity in 1 cat, adverse food reaction in 1 cat, and concurrent environment and adverse food reaction in 1 cat). Medical conditions can lead to stress and anxiety and associated behavior problems (e.g. self-trauma, predisposition to development of a compulsive disorder). In fact, anxiety might contribute to pruritus in humans, since stress can lead to an increase in cytokines, release of opioids, serotonin and other vasoactive peptides, especially in atopic individuals.[18-21]

The hypothesis for the pathogenesis of canine (and human) atopic dermatitis is that a putative epidermal barrier defect could facilitate the contact of environmental allergens and microbes with epidermal immune cells at skin sites. [22-23] As mentioned above, a link has also been found between stress and an impairment of epidermal barrier homeostasis.[3-4] One might hypothesize that stress could therefore exacerbate atopy. Put another way, might the "uptight atopic pet" have a lower threshold to the discomfort, a barrier defect and a stress induced barrier recovery defect that exacerbates or extends the duration of the condition? Opioid peptides released during stress may even further potentiate pruritus.[24]

GENETICS

Genetics may play a role in the expression of displacement and compulsive behaviors in certain cats.[7] For example, psychogenic alopecia has been reported to be more common in the Oriental breeds.[24-25] Interestingly, 3 of the 5 cats with psychogenic alopecia in the present study were Oriental breeds or their crosses. Alternatively, Siamese and their crosses may also be predisposed to adverse food reactions, which might have a similar pattern of hair loss, further complicating the diagnostic process.[24-25]

Key Clinical Diagnostic Points:

- Many cats presented with feline alopecia have an adverse food reaction as part of their condition
- In many cases, the underlying causes are multifactorial
- A normal skin biopsy does not rule out a medical cause of the self trauma
- It is possible to have both a medical and behavioral problem, and both need to be addressed for successful management
- Psychogenic alopecia is over diagnosed (cost playing a role?)

THERAPY

MEDICAL THERAPY

Medical therapy should be directed against the underlying etiology, of course. Fungal disease should be eliminated. Parasites must be well controlled. When an adverse food reaction is identified, the ideal treatment would include identification of the particular offending ingredient(s) and its avoidance. As multiple etiologies often play a role, one may need to control the environmental component while concurrently managing the diet. If the patient suffers from "catopy", allergy testing can be considered. Allergen specific immunotherapy, steroids and cyclosporine are the mainstay treatments for many of these patients. Whenever possible, I use oral steroids in lieu of injectable steroids in the treatment of pruritus. I believe that I get a better response to prednisolone when compared to prednisone in cats. Indeed, better bioavailability has been reported.[26] I have found that antihistamines have a role to play in some patients with "catopy" . Like fatty acids, they can help to decrease doses of the more offensive therapies. However, I don't find that antihistamines do a good job of "putting out the fire", and I use these products to hold the patients once steroids are on board or to help reduce the steroid dose or frequency.

BEHAVIORAL THERAPY

Patients with true psychogenic alopecia need behavioral therapy (see Dr. Landsberg's talk in these proceedings). As is the case for all behavioral conditions it isn't only about drugs. One needs to consider the possibility of an underlying stressor as an initiating or perpetuating factor and so it is important to decrease stress. As with zoo animals, enrichment leads to decreased stress and decreased stereotypic behaviors. Further information can be found in the Feline Behavior Guidelines from the American Association of Feline Practitioners: (www.catvets.com/uploads/PDF/Feline_Behavior_Guidelines.pdf), or The Ohio State behavior guidelines (www.vet.ohio-state.edu/indoorcat)

Important behavioral therapy concepts:

- Working for food – multiple canned meals, hiding dry food in toys, higher protein diets to more simulate "canned mouse"
- Increase playing opportunities
- Household enrichment – perches, places to explore, provide a regular sleeping area
- Feliway (cat facial pheromones)

Drugs should be a last resort but may be needed if the condition has progressed to a compulsive disorder (where a "loop is set-up"), at least in the beginning. Clomipramine is a good option in most cases. Once all the hair is back (and if all abnormal licking seems to have ceased), continue the environmental treatment and the Feliway and then (if you do sufficient behavior therapy and treat any concurrent medical) try to get the cats off medication. Anxiety induced alopecia and those where the initiating factors are under control might stay improved, but a compulsive disorder (especially if there is a genetic component) may need long term drugs. Clomipramine should be avoided in cardiac cases or cats with potential for urinary tract obstructions. Fluoxetine may be preferred in this cases.[27]

In our study, the alopecia improved dramatically in the 2 PA cats with a combination of behavioral management (primarily consisting of a more predictable daily routine with attention to increasing enrichment through social play sessions and introduction of new play toys) and clomipramine treatment. One of the cats also had hyperesthesia, which improved dramatically with treatment. Of the 3 cats with partial psychogenic alopecia, 1 responded to behavioral management, 1 was lost to follow-up, and 1 was not treated.

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NOTES

ADVANCES IN VETERINARY DERMATOLOGY: PAST MILESTONES & FUTURE PREDICTIONS

Ihrke, PJ
Department of Medicine & Epidemiology
School of Veterinary Medicine, University of California,
Davis, California, U.S.A.

A. Introduction

1. This presentation and the written material provided in the NAVDF Proceedings are derived from and adapted for a different audience from the Hill's Excellence in Veterinary Healthcare Award Lecture presented at the World Small Animal Veterinary Association (WSAVA) World Congress in Sao Paulo, Brazil in July of 2009[1]. Although given during the 'continuing education' concurrent sessions, this presentation is not intended to be either a continuing education or research presentation.
2. The goal will be to review the 'Top 10' advances, milestones, or catalysts that have advanced veterinary dermatology in our modern age plus to attempt to predict the next generation of key future developments that may revolutionize or jump-start another era.
3. Material presented will be a compilation of my personal thoughts and predictions plus those of our vibrant and active international community in veterinary dermatology. As a method of seeking this input, I sent out a request for suggestions on the milestones from our past and the predictions for our future on the VetDerm Listserv and the ACVD DipDerm.

B. Brief Overview of the Past

1. Veterinary dermatology has changed and advanced unbelievably since initial modern development 35 years ago. The modern age began in 1974 when a Dermatology Specialty Group was granted permission under the umbrella of the American College of Veterinary Internal Medicine (ACVIM) to form a certifying college in dermatology. In 1982, the Dermatology Specialty Group of the ACVIM was granted permission to become the American College of Veterinary Dermatology (ACVD) as a free-standing specialty College. Subsequently, the European College of Veterinary Dermatology (ECVD) was formed in 1992, the Dermatology Chapter of the Australian College of Veterinary Scientists (ACVSc), was formed in 2002, and the Asian College of Veterinary Dermatology (AiCVD) was formed in 2005.
2. Specialty Colleges in dermatology have expanded hugely since their inception. As an example, the ACVIM Dermatology/ACVD began with 13 charter Diplomates and now has a membership of over 200. Similar advances are occurring world wide.
3. This same time period has seen the rapid rise of organized veterinary dermatology internationally.

C. Top Ten Advances of Veterinary Dermatology

- Broadly, these advances can be grouped into organization, development, and education; communication; and research and technology. All of these advances are intertwined.

1. **Organizational and global development** – Veterinary dermatology achieved a 'critical mass'. Simultaneous and sequential political developments globally lead to the formation of strong national specialty organizations that fostered the establishment of specialty certifying colleges around the world.
   a. Universities and certifying colleges initiated the development of dermatology residency training programs leading to credentials for board certification.
   b. Cross pollination occurred between dermatology academies and societies globally and more dermatologists traveled and attended and participated in the meetings of other groups.
   c. Strong regional and national associations lead to the collaborative establishment of World Congresses of Veterinary Dermatology (WCVD-1 in 1989 in France, WCVD-6 in Hong Kong in 2008) and an organization that shepherded these world congresses (WCVDA).

   d. Strong support of basic and applied clinical research has resulted from this organizational explosion.
2. **Emergence of dermatopathology** – The gradual development of a 'critical mass' in dermatopathology was fostered by the joint interest globally of pathologists and clinical dermatologists towards advancing the understanding of the pathology of skin disease and sorting out diseases based on skin biopsy.
   a. **International Society of Veterinary Dermatopathology (ISVD)** – This first true international sub-specialty group composed of pathologists and clinicians worked with clinical dermatology to advance the science and art of skin pathology.
   b. Dermatopathology has become a crucial arena for research and has lead directly to the description of many 'new' skin diseases.
3. **Communication – International cooperation and information exchange** – Internet listservs have lead to improved understanding of disease pathogenesis, diagnosis, and treatment via the rapid ability to access the thoughts and experiences of others.
   a. **International Veterinary Dermatology (VetDerm) ListServ** – The establishment of this listserv connected the international dermatology community on a daily basis. Any veterinarian with internet connection suddenly could communicate with others interested in the discipline globally.
   b. **ISVD ListServ** – Now pathologists and dermatologists could communicate rapidly about both concepts and actual cases.
   c. Near immediate access to published literature via the web.
4. **Digital imaging** – Dermatology is one of the most visual clinical disciplines. World-changing advancements in the generation, manipulation, and sharing of digital images has lead to an unprecedented leap in international visual communication.
   a. Individual compressed digital clinical and histopathologic images are shared daily on the VetDerm and ISVD Listservs.
   b. Entire digital presentations can be shared at meetings and via downloading websites.
5. **The Journal – Veterinary Dermatology** – Dermatology came of age with the birth of an international refereed journal in 1989 devoted entirely to dermatology[2]. Our debt of gratitude for this vision and wisdom is enormous.
6. **Partnership with The Veterinary Pharmaceutical and Pet Food Industry** - The crucial recognition of the importance of this partnership has lead to more rapid advances in research (industry, university, specialty practice), and the support needed for local, regional, regional, national, and global congresses.
   a. Strong support of basic and applied clinical research has resulted from this collaboration.
   b. Regional and global congresses could not exist without industry support; meeting costs have become too high.
7. **Recognition of *Malassezia spp*. as a major cause of disease and pruritus** – This quantum leap in our ability to understand and manage pruritic animals (especially dogs) was mentioned as key by almost all of dermatologists that responded to the listserv survey. The publication of a paper in 1983 and the 'rediscovery and advancement' of this concept in 1987 changed the way veterinary dermatology will be practiced forever[3, 4].
8. **Understanding of cat flea biology and modern flea control** – Research on the life cycle of the cat flea leading to knowledge that the adult is an obligate ectoparasite led to a paradigm shift in understanding fleas.
   a. Giant and then incremental advances in our understanding of the cat flea and flea allergy have revolutionized flea management. Similar to other hypersensitivities, flea allergy is yet another dose-dependent hypersensitivity with a continuum of clinical signs reflecting dose of antigen injected and magnitude of hypersensitivity.
   b. Understanding of the cat flea life cycle aided in development of the superb modern products now available for flea control.

9. **Research breakthroughs in our understanding of key diseases** –
    a. **Understanding of atopic dermatitis** – From the initial identification of canine IgE to current knowledge, this difficult disease has become one of the better understood diseases in veterinary medicine. The ACVD evidence-based medicine taskforce brought all of the information together in a special issue of Veterinary Immunology and Immunopathology published in 2001[5,6].
    b. **Increasing our knowledge of staphylococcal skin disease**, (especially in dogs) – Incremental research has improved our understanding of pyoderma. Although the mechanisms still elude us. Why is secondary bacterial pyoderma so common in the dog in comparison to all other species studied?
    c. **Characterization of auto-immune skin diseases -** Understanding increased dramatically through research characterizing antigens and mechanisms of disease[7].
    d. **Understanding otitis externa** – Recognition of the importance of underlying disease, and predisposing and perpetuating causes of ear disease in the dog was crucial to recognition of underlying triggers and better management success.
    e. **Key Techniques -** Laboratory tools have changed our ability to diagnose diseases and identify micro-organisms. The development of the radioimmunoassay (RIA) for peptide hormones was the forerunner of antibody-based assays. Polymerase chain reaction (PCR) has allowed us to detect micro-organisms and fractions of micro-organisms in diseased as well as seemingly normal skin.
10. **New products that changed our management of key diseases** – New drugs and devices revolutionized management of skin diseases.
    a. **Avermectins and ivermectin** – Before avermectins and milbemycins, canine demodicosis was poorly responsive to therapy. Avermectins also became drugs of choice for the management of contagious mite infestations such as canine scabies.
    b. **Topical therapy** – Development of shampoos, rinses, and sprays especially designed for animals has lead to increased management success and enhanced quality of life.
    c. **New flea products and new delivery systems** – Development of insect growth hormone regulators and new parasiticides including spot-on topicals, and oral and topical systemics with more rapid speed of kill and greater residual activity provided us with products with wider margins of safety, less toxicity, greater efficacy, and much greater likelihood of owner compliance.
    d. **New antibiotics and new regimens** – New antibiotics with regimens offering the promise of less frequent dosing and better owner compliance are now available.
    e. **New antifungal medications** – Development of new, safer medications for surface and deeper infection made previously untreatable or difficult-to-treat diseases now treatable.
    f. **Cyclosporin** – This drug clearly has altered how we can manage allergic and other immunologically mediated skin diseases.
    g. **Quality commercial elimination diets** – Specialty diets have greatly improved our ability to achieve owner compliance and diagnose adverse reactions to food. Both limited antigen diets and hydrolyzed diets offer better choices beyond home cooking.
    h. **Video-Otoscopy** – The advent of the video otoscope increased our understanding of and ability to diagnose and manage otitis externa and otitis media.
    i. **Allergen Specific IgE Serology** – Improvement in *in vitro* allergy testing enhanced our ability to select appropriate allergens for allergen specific immunotherapy.

D. Top 10 Future Predictions for Advances in Veterinary Dermatology – My colleague, Stephen White reminded me of an old joke in which Nostradamus supposedly said 'The hardest thing to predict is the future'. Not surprisingly, our colleagues all showed greater reluctance to predict the future in comparison to offering opinions on key past advances.

1. **Sequencing of Domestic Animal Genomes** – The new age of genetics and genomics aided by the sequencing of the canine, feline, and equine genome should usher in a new era of pharmacogenetics. Epidemiologic studies will lead to discovery of disease genes and modifier genes amenable to gene therapy. These breakthroughs should allow us to estimate genetic probability of individual animals developing specific diseases.
2. **Antimicrobial Resistance, Methicillin Resistant Staphylococci and the war on infectious diseases** - The World Health Organization has identified antimicrobial resistance as one of the 10 biggest threats to human health. The same concern applies to animal patients, especially in dermatology[8]. We must use antimicrobials wisely in all species or attempts will be made to limit veterinary access to antimicrobials, new and old. Empirical therapy for managing bacterial skin diseases (especially after initial failure) may become a thing of the past. Topical therapy with agents with novel modes of activity may offer one future answer. Manipulation of environmental and other underlying factors may play a larger role in prevention and therapy. Study of quorum sensing and biofilms may lead to new treatment options for otitis externa, mucocutaneous pyoderma, and deep bacterial infection with fistulous tracts and tissue undermining.
3. **The Rise of Evidence-Based Medicine –** The demand for reasonable proof rather than clinical conjecture will alter how research studies are performed and how and if results are published. Data will be based on more than simply clinical impression.
4. **Advances in the Study of Drugs** – Improved assays will be much more sensitive and selective and techniques such as computer modeling for pharmacokinetics will be easier. These advances will increase the speed of availability of new agents for clinical trials, if funds remain available for veterinary pharmaceutical research. The key concepts of the 'mutant selection window hypothesis' and the 'mutant prevention concentration' may allow more appropriate antibacterial therapy with diminished likelihood of resistance.
5. **Availability of New and Better Drugs** – Advances in the efficiency and productivity of drug studies will lead to new drugs and delivery systems. Owner compliance will be enhanced by drugs with greater residual activity or other methods of slow drug releases.
6. **Improved Understanding of Canine Pyoderma** – Pyoderma is second only to flea allergy dermatitis as a cause of small animal skin disease. Yet, we still do not know why pyoderma is more common in dogs than in any other mammalian species studied. What causes pyoderma? What is the defect in the dog?
7. **Better Diagnostic and Therapeutic Immunology Support for Clinical Medicine** – Our abilities to determine inadequate immune response to skin pathogens are still rudimentary. Better understanding of the immunology of infection could lead to development of more effective immunostimulants. New biological therapies such as monoclonal antibodies or receptor mimics used in the treatment of rheumatoid arthritis, other immunologic disorders, and cancer are being developed in human medicine. This may lead to development of more specific and less toxic therapy at the molecular level for animal diseases as diverse as auto-immune disease, atopic dermatitis, and cancer. We may learn how to manipulate immune responses to prevent or cure diseases.
8. **Safe and Effective Anti-Itch Drugs** – Despite many years of attempts, anti-pruritic drugs more effective than corticosteroids still are not available. Cyclosporin may be better than many previous developments, but it is not the perfect drug. Dermatology would be revolutionized if safe, effective, and reasonably priced anti-itch medications were developed.
9. **Future Developments in Immunotherapy for Atopic Dermatitis** – Will immunotherapy be refined based on more reliable allergy testing? Will the process of immunotherapy be 'modernized' with anti-IgE therapy or DNA adjuvants? Would the development of safe and effective anti-itch drugs kill immunotherapy?

10. **The Biggest Threat to the Advancement of Veterinary Dermatology?** – The major threat on the horizon is the relatively small group of people globally doing basic and applied research in dermatology and related fields. Research is poorly funded and becoming more expensive. This threat was of greatest concern to our global group. Breakthrough areas such as stem cell therapy, gene therapy, and monoclonal antibody therapy are hugely expensive. Our resources will never be comparable to those in human medicine. Astute clinical observations may provide the leaps not provided by funding. Fortunately, we do have excellent new talent entering the field.

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