Anatomy, physiology and pathophysiology of the ear that you must know

Rod A.W. Rosychuk, DVM, DACVIM

Colorado State University, Ft. Collins, Colorado, USA

PINNAE

1. Inter-gragic incisure. This is a “notch” on the caudo-lateral entrance to the vertical canal that is a very helpful groove in which to put the tip of an otoscope or video otoscope head to initiate an otoscopic examination. This is a less sensitive area of the ear that allows for stabilization of the otoscope cone prior to advancing for deeper visualization of the ear.

EXTERNAL EAR CANALS

1. Luminal fold. This is a fold of the lining of the ear canal on the dorsal aspect of the junction of the vertical and the horizontal canal. “Bumping” up against the luminal fold with the tip of an otoscope cone often results in a painful response on the part of the patient. With the patient in sternal recumbency, the luminal fold can be minimized by pulling the pinna up and out from the base of the skull. When the patient is in lateral recumbency, the luminal fold is minimized by pulling the pinna vertically. The luminal fold is less prominent in the cat.

2. Make-up of the lining of the ear canal. The ear canals are lined by skin containing hair follicles, sebaceous glands in the superficial dermis and fewer small ceruminous glands (modified apocrine glands) in the deeper dermis. Hair follicle density and the length of hairs along the canal walls varies with the breed of dog. Moderate to large amounts of long hair may be seen throughout the canals in breeds such as the poodle, Bichon frees, Airedale and Schnauzer. In all breeds of dogs, hairs may be seen growing on the floor of the horizontal canal, adjacent to the tympanic membrane (TM) (just in front of the tympanic membrane). They are of variable length. They often trap a small amount of wax that is considered a “normal” finding in the ear (i.e. normal to find a small amount of wax accumulated on the floor of the horizontal canal, just in front of the TM). These hairs help to provide appropriate orientation when working in the ear with a video otoscope (i.e. they are always located ventrally).

3. Cerumen (ear wax) consists of desquamated corneocytes (epithelial cells), ceruminous and sebaceous gland secretions. It is a mixture of proteins, lipids, amino acids and mineral ions. In the normal dog and cat, wax is not seen accumulating on the walls of the canals. However, in the normal dog, it is quite common to see a small amount of wax on the floor of the horizontal canal, just in front of the TM. This accumulation is likely facilitated by the acute angle formed between the floor of the horizontal canal and tympanum and the hairs that normally grow in this area that ‘trap’ the wax. This accumulation is not seen in the normal cat. Anything that causes irritation or inflammation within the ears will result in increases in wax production. The degree of hydration of the ear wax will often contribute significantly to its color (e.g. drier wax tends to be darker).
4. How does the ear clean itself? The self cleaning function of the canals is facilitated through a process of lateral epithelial migration. Epithelial cells are noted to grow laterally from the tympanum. They start from the area around the manubrium or “handle” of the malleus and move over the tympanum and then down the canals of the ear. They carry debris with them. This cleansing system appears to be easily overwhelmed/inadequately functional with inflammatory ear disease.

5. Normal bacterial and yeast flora of the ear canals: There is a normal bacterial and fungal flora of the canine and feline ear canal. In drier environments, such as Colorado, this consists of an occasional Malassezia and/or cocci (usually *staphylococcus* sp.) per oil immersion field. This natural carriage does vary with the environment - potentially higher numbers being seen in normal ears in more humid environments.

**TYMPANIC MEMBRANE**

The tympanic membrane of the dog is made up of the pars flaccida and pars tensa. The pars flaccida is a small area of the dorsol to antero-dorsal region of the tympanum which is relatively flaccid and vascular. This structure may dilate (“out-pouch” or “bulge”), in association with increases in air pressure within the middle ear. The “bulging” pars flaccida is likely a pressure release system for the middle ear. The finding of an air filled, dilated pars flaccida is likely of no real clinical significance. The pars flaccida may also dilate as it fills with exudate and/or debris from an otitis media. Cats do have a pars flaccida, but it is not readily visible and usually does not dilate in normal cats, as is seen in normal dogs. It can occasionally be seen to dilate with exudate in the presence of an otitis media. It can also become inflamed, usually in the presence of an otitis media (myringitis). A normal pars tensa is translucent, with striations seen extending from the manubrium of the malleus outward to the periphery. Some of this translucency is lost as the individual ages. The manubrium (handle) of the malleus is the white, curved structure located over the antero - mid portion of the tympanum. The open end of the curved handle of the malleus points towards the nose. In the cat, the handle of the malleus is much straighter than in the dog. The epithelium of the tympanum grow outwards from the area around the handle of the manubrium. This outward growth occurs in a radial pattern. The epithelium of the pars flaccida grows faster than that of the pars tensa. Permanent damage to the manubrium of the malleus and/or the pars flaccida precludes healing of a perforated pars tensa. Assuming the area around the handle of the malleus and the pars flaccida remain viable, following complete destruction of the pars tensa in normal dogs, complete regrowth is noted within 21-35 days. In the dog, a whitish appearing diffuse “line” can sometimes be seen through the tympanic membrane. This is the bulla septum of the middle ear which marks the separation of the tympanic cavity from the tympanic bulla. It usually requires the magnification offered by a video otoscope to see this structure. This structure is not seen in the cat.

The tympanum is oriented at about a 30-45 degree angle from perpendicular (dorsal to ventral; dorsal closer to the otoscopist than the ventral aspect).
In the dog, the tympanum can be forced into the tympanic cavity, usually as a result of chronic, progressive pressure exerted by accumulated wax and debris within the horizontal canal. After a deep ear cleaning, this may be seen as a tympanum that is deeper in the horizontal canal than the normal contralateral side. When the tympanum has been severely pushed in to the middle ear, looking deep within the horizontal canal using a conventional otoscope may only show a dark hole, suggesting that the tympanum is not intact. This appearance (a dark, black hole) has been referred to as the “false” middle ear (i.e. giving the impression that the tympanum has been perforated and the observer is looking into the middle ear when the tympanum is really intact, but pushed in to the middle ear). When there is a “false middle ear”, the intact nature of the tympanum can usually be appreciated with a video otoscope (greater magnification). Through a conventional otoscope, the dark hole can be probed with a firm catheter. If the firmness of “bone” is felt, it is assumed the tympanic cavity is perforated. If palpation with the catheter “tip” is soft, it is assumed that the tympanic cavity is still intact. With most moderately severe “false middle ears”, once debris has been removed from the ear, the tympanum generally returns to its more normal position within about 1-2 weeks. Note: the tympanum of the cat usually does not have the “give” that is seen in the dog. Pressure brought to bear against the feline tympanum much more readily results in perforation.

On occasion, if the tympanic membrane or parts thereof are pushed in to the middle ear (by debris), this may result in the development of a cholesteatoma. Cholesteatomas are usually seen in ears that have severe, chronic proliferative changes and stenosis of the horizontal canals. The adhesion of pieces of the tympanic membrane to the inflamed middle ear mucosa results in the subsequent shedding of large amounts of epithelial debris into the tympanum space, eventually creating a “mass” effect. In one study, cholesteatomas were noted to form in 7 of 62 dogs with chronic otitis externa. Severe stenosis of the horizontal canals was noted in all of these affected patients. Calcification of the auricular cartilage was noted in 6 of 7.

**CANINE AND FELINE MIDDLE EAR**

**Canine middle ear**

The middle ear, starting from dorsal to ventral is made up of the epitympanic recess which houses the three small middle ear bones (malleus which is attached to the tympanic membrane, incus and stapes which is attached to the oval (vestibular) window leading to the inner ear. The oval window is dorsal and fairly central in the epitympanic recess. The tympanic cavity is that area of the middle ear just inside the tympanum (mesotympanic cavity). The medial surface of the tympanic cavity is made up of bone; specifically the barrel shaped, cochlear promontory. The cochlea (responsible for hearing) sits within this structure. At the caudal end of the promontory is the cochlear (round) window which communicates with the bony labarynthe of the cochlea. This structure is dorsao-caudal in the tympanic cavity. The round window is only covered by a thin epithelial lining. Access of drugs, inflammation
and infection from the middle ear to the inner ear structures is made possible by passage through the oval and round windows. The opening of the auditory tube (eustachian tube) lies in a rostro-medial location in the tympanic cavity. It opens in to the nasopharynx and serves to equalize pressure across the tympanum. Beneath the tympanic cavity is the large tympanic bulla. The tympanic cavity and the bulla are separated by a partial bony ridge - the bulla septum. The leading edge of this ridge is often noted to have variably sized bony spicules. The tympanic cavity of the middle ear is covered by ciliated respiratory epithelium that contains goblet cells. There is a continuous production of small amounts of fluid from this respiratory epithelium that empties through the auditory canal. This is the natural flushing mechanism of the middle ear. The lining of the tympanic bulla is more squamous (non ciliated). The middle ear has a normal bacterial flora. Obstruction of the auditory canal results in the accumulation of secretions in the middle ear (variable consistencies). Sympathetic nerves run across the more dorsal aspect of the medial wall of the middle ear, over the upper part of the cochlear prominence. The facial and parasympathetic nerves run over the most dorsal aspect of the medial wall of the middle ear. For much of their passage through the middle ear, they are in a bony channel. However, for a short distance, they are not covered by bone and are therefore prone to damage in the presence of otitis media.

**Feline Middle Ear**

In the cat, the middle ear is divided in to a smaller dorso-lateral chamber that consists of the epitympanic recess and tympanic cavity, much as in the dog. However, the larger ventro-medial bulla is separated from this upper chamber by an almost complete, thin, bony septum. The communication between the dorso-lateral and ventro-medial chambers is limited to a long, thin “slit” adjacent to the medial wall of the middle ear which becomes a small “hole” at the caudal most aspect of the septum. The round window (cochlear window) is just adjacent to this opening. The sympathetic nerve plexus courses over the medial wall of the middle ear (cochlear promontory) and extends more ventrally than in the dog (just above the “half way” line bisecting the medial bony wall of the middle ear). The facial nerve runs dorsally in the epitympanic recess, through a bony channel and is therefore relatively resistant to damage in association with otitis media (unless the process causes bony lysis). As in the dog, the tympanic cavity is covered by a mucous producing, ciliated respiratory epithelium. The middle ear has a normal bacterial flora. Obstruction of the auditory canal results in the accumulation of mucoid secretions in the middle ear. These accumulations tend to be quite thick (more mucoid than in the dog).

**INNER EAR**

The inner ear is made up of various tubular and spiral cavities within the petrous temporal bone that contain the cochlea (hearing) and the semicircular canals (balance). Sound waves in the external ear canal → vibrations of TM → vibrations through the malleus, incus and stapes to the oval window → vibrations transmitted into the fluid within the cochlea → hair cell stimulation in the organ of Corti → nerve impulses → brain (sensed as sound). Interesting facts regarding hearing:
1. Hearing is only partially lost in an ear when there is a hole in the tympanum.

2. “Tip off” to complete loss of hearing in one ear - individual can still hear, but loses the ability to localize sound.

3. Ototoxic agents access the inner ear from the middle ear through the round (cochlear) and/or oval (vestibular) windows and most commonly cause hearing loss or deafness through their effects on cochlear hair cells.

4. Deafness: congenital cochlear dysfunction as with Dalmations, white cats; aging may result in inner ear dysfunction of various types. The accumulation of significant amounts of debris within the external ear canals or middle ears may result in a significant reduction in hearing (sound conduction deficits).

Damage to the vestibular apparati result in ataxia, head tilt, nystagmus, positional strabismus (deviation of the eye) and nausea.

**PATHOPHYSIOLOGY OF OTITIS EXTERNA**

The pathologic changes associated with otitis externa in many ways tend to be relatively similar, regardless of the underlying primary cause. However, the degree of change (e.g. ceruminous gland hyperplasia, ectasia and fibrosis) may vary with breed. With acute otitis, there is edema and inflammatory cell infiltrates in the dermis. With chronicity, the epidermis becomes hyperplastic (thickened). Ceruminous glands dilate and fill with secretions. They may appear as small “bumps” - a cobblestone appearance - on surface of the canals. As they enlarge, they contribute to thickening of the dermis. As they enlarge, ceruminous glands may rupture, which may also contribute to inflammation. Sebaceous glands tend to vary with respect to their response to chronic inflammation. Numbers/size may increase, decrease or remain the same. Variable degrees of fibrosis may develop in the dermis.

With chronic otitis, it would appear that the cocker spaniel is more likely to develop ceruminous gland hyperplasia and dilatation (ectasia) and have relatively less fibrosis. In other breeds, dermal fibrosis tends to predominate. When ceruminous glands become very dilated or undergo neoplastic transformation (ceruminous adenoma or adenocarcinoma), the accumulated secretions often make them appear bluish in color.

Secondary bacterial infections may produce an epidermitis, folliculitis or furunculosis. Furunculosis contributes to dermal expansion and subsequent decrease in size of the canal lumen (i.e. stenosis of canals). In some individuals, the lining of the ear canal may be thrown in to folds which occlude the canals. In others, fibroproliferative nodules may develop. This tends to be seen more commonly in the Spaniel breeds. With severe, chronic, deep seated inflammation, there is a tendency to have the auricular cartilage and surrounding soft tissue calcify and ossify. The cocker spaniel tends to develop soft tissue calcification/ossification more rapidly and frequently than other breeds.
Diagnosis of otitis externa and otitis media; selection and interpretation of diagnostic techniques for ear diseases

Rod A.W. Rosychuk, DVM, DACVIM
Colorado State University, Ft. Collins, Colorado

Establishing a diagnosis for individuals presented with otitis externa and/or otitis media requires an understanding of the etiologies and pathogenesis of these diseases.

OTITIS EXTERNA

We recognize several factors that contribute to the development of the problem. They include primary, secondary, predisposing and perpetuating factors.

Canine

Primary Factors: those that initiate otitis
1. Allergies (atopy, food sensitivity). These represent the most common primary factors.
2. Ear mites.
3. Foreign bodies such as grass awns etc.
4. Hypothyroidism and idiopathic primary seborrhea. These problems produce a ceruminous otitis (waxy, mildly inflamed ears).
5. Autoimmune disease. The most common to produce otitis is pemphigus foliaceus.
6. Zinc responsive dermatosis
7. Sebaceous adenitis
8. Masses within ears include neoplasia (most commonly ceruminous adenomas, less commonly ceruminous adenocarcinomas), polyps (growing from the walls of the canals) and ceruminous cysts.

Secondary factors: contribute to inflammation within the ears and consist of secondary infections.
1. Malassezia: the most common secondary infection seen. Individuals may develop hypersensitivities to Malassezia which also may contribute to the inflammation seen with these infections
2. Bacteria: with both acute and chronic otitis, the most common secondary bacterial infection is with staphylococci (usually *staphylococcus pseudintermedius*). Chronic otitis also selects for gram negative (“rod” shaped) bacterial infections (*Pseudomonas, Proteus, Klebsiella, E. coli, Corynebacterium*).
**Predisposing Factors:** noted to amplify the signs of otitis, but, by themselves do not cause otitis.

1. **Anatomic predispositions:**
   a. floppy ears (decrease aeration, increase humidity)
   b. hair in canals (trap waxy debris and exudates)
   c. stenotic horizontal canals adjacent to the tympanic membranes as seen in brachycephalic breeds (ear more rapidly filled with wax and debris with allergic otitis)

2. **Environmental predispositions:**
   a. higher environmental relative humidity - elevates humidity in ears
   b. increased moisture in ears (swimming; macerates lining of ear canals).

**Perpetuating factors:** keep inflammation going within ears.

1. Proliferative changes within the canals (thickening/roughening of the canal walls; excessive folding of canal walls; fibroproliferative nodules) - all provide microenvironments that promote secondary infections and the entrapment of debris that is potentially irritating and also a nidus for infection
2. Otitis media - can serve as a reservoir for secondary infections that continue to populate the canals through a perforated tympanic membrane.
3. Overtreatment: keeping an ear too moist results in the accumulation of large amounts of whitish, opalescent epithelial debris
4. Under-treatment
5. Reactions to topical medications (e.g. propylene glycol, neomycin).

**Feline**

**Feline primary factors:**

1. Ear mites: the most common primary factor
2. Allergies: atopy, food sensitivity
3. Foreign bodies
4. Idiopathic ceruminous otitis - although suspect most of these are just milder allergic disease
5. Proliferative and Necrotizing Otitis Externa of Cats
6. Aural polyps
7. Ceruminous cysts
8. Neoplasia: primarily ceruminous adenocarcinoma/adenoma (carcinoma more common)

The most common secondary factors in the cat are Malassezia, with a lesser incidence of bacteria (most commonly *staphylococcus* spp.). Gram negative bacteria tend to be found much less commonly in the cat than in the dog. Perpetuating factors include otitis media, overtreatment, under-treatment and reactions to topical medications (e.g. propylene glycol, neomycin).
Canine Otitis Media

Otitis media in the dog is most commonly related to perforation of the tympanic membrane (TM) and extension from an otitis externa. It may be either infectious (bacterial and/or Malassezia that come from the canals) or non infectious (waxy debris that enters the middle ear; foreign bodies). Scenarios that increase the potential for perforation of the TM include:

1. Pseudomonas infections have been associated with a higher incidence of perforation. Affected ears are usually severely inflamed, +/- ulceration, +/- greenish “slimy” exudate
2. Severely stenotic horizontal canals associated with chronic, proliferative otitis. 50-80% will have perforated TMs due to debris building up within the canals that cannot get out of the canals - put pressure on the TM and eventually perforate the TM
3. Masses (cysts, neoplasia, polyps) that completely occlude the canal result in wax and epithelial debris accumulating behind the mass that put pressure on the TM and may eventually perforate the TM.

Other relatively rare causes of otitis media in the dog are ascending infections (up the auditory tube). In these instances, the TM will be intact. The pars flaccida may be dilated and filled with inflammatory debris.

Feline Otitis Media:

1. Auditory tube dysfunction and/or ascending infections (up the auditory tube); tympanum will be intact
   a. Obstruction of the auditory tube (Eustachian tube) due to inflammation (rhinitis, posterior pharyngitis) and less commonly neoplasia. As a result of this, the mucoid fluid that is normally produced and empties through the auditory canal as part of the normal flushing mechanism if the middle ear accumulates within the middle ear. In this “closed system” air is absorbed, producing negative pressure that also promotes increased mucoid secretions. Fluid may be either non inflammatory (usually with more acute accumulations) or inflammatory (becomes more inflammatory with chronicity) and sterile. These fluid accumulations are usually found as incidental findings on radiographs, CT or MRI. They are usually not associated with clinical signs (including neurologic signs). However, inflammatory fluid accumulations associated with obstruction may also be infected (bacterial infection). The source of bacterial infection may be the normal flora of the middle ear (bacteria are normally present within the middle ear of a small percentage of normal cats at any given time). Bacterial otitis media is often associated with clinical signs, including neurologic signs of otitis media and interna.
   b. Dysfunction of auditory tube - does not close normally; ascending infection; fluids that accumulate are inflammatory; bacteria are present. Clinical signs are often present (including neurologic signs of otitis media/interna. Tympanum will be intact
2. “Primary” otitis media - inflammatory accumulation of fluid within the middle ear that, to the best of our knowledge, is not associated with auditory tube dysfunction and is not bacterial. Some feel this may be a viral problem (although viruses have not been found to date). This problem is heralded by the acute development of the neurologic signs of otitis media/interna. Tympanum will be intact.

3. Extension from an otitis externa through a perforated tympanum. Less common. This is most commonly associated with the accumulation of hard concretions of wax that accumulate within the ear canal secondary to allergy or ear mite problems (ceruminoliths), or the accumulation of debris behind masses that fill the canal (ceruminous cysts, neoplasia).

4. Aural polyps: idiopathic inflammatory lesions that predominantly originate from the dorsolateral chamber of the middle ear.

**Diagnostic Techniques for Otitis Externa**

Diagnostic steps that are considered mandatory when establishing the pathogenesis of otitis externa include notation of signalment and history, performing a thorough general dermatologic examination, a thorough examination of the face (pupil size, facial nerve function; opening mouth to assess for bulla pain) and pinnae (including palpation of ear canals for evidence of ossification), otoscopy or video otoscopy and cytology. Those diagnostics that are more variably required include culture and sensitivity testing, imaging (radiographs, CT and/or MRI) and biopsy and histopathology.

**Otoscopy:** May allow for the diagnosis of ear mites, ticks, foreign bodies; assess distribution of disease, degree of inflammation, stenosis, proliferative changes, amount and nature of wax/exudate in ears and the appearance and integrity of the tympanum. Keep records of changes noted, especially in chronic or recurrent cases. The author uses a 4 mm polypropylene specula for all routine examinations in both the dog and cat. This allows for the visualization of the tympanum in all but the largest of dogs. The otoscope must have enough light to visualize to the depths of the ear. If the otoscope light is adequate, you should not be able to look in to it (too bright). If the light is too dim, the problem could either be with the power source or bulb. Proper restraint is essential. In dogs, have the restrainor direct the muzzle slightly into the thorax. Pinna should be pulled up and out from the base of the skull by the otoscopist. This tends to minimize the angle that must be negotiated at the junction of the vertical and horizontal canals. Place the tip of the otoscope cone in the intertragic incisure as a good starting off spot for your examination. Visualize as you progress down the vertical canal, then move the scope horizontally to visualize in to the horizontal canal. For cats, restraint is usually minimal; restrainor holds shoulders/back to keep cat from moving. The otoscopist pulls the pinna up and out with significant force (which has an immobilizing effect on the cat). For dogs or cats who do not tolerate otoscopy, strong consideration should be given to sedation. Otoscopy should be performed before cytologic examination (which may push debris into the canals and obscure
visualization). If debris is obscuring visualization at the onset of the examination, pass a swab into canal, then re-evaluate. Video otoscopy allows for better visualization of pathology (much greater magnification). It is ideal to perform a video otoscopic examination while in the examination room for all patients with otic pathology. The owners are able to visualize these changes which enhances compliance with therapy. Pictures of the ears can be saved for the patients’ records and used as a source of comparison at future visits.

Data from otoscopic examinations allows for decisions about the need for otic cleansers and the frequencies of their use (based on the amount of wax seen in the ears); the need for hair removal from the canal as part of the “ear cleaning”; the need for more aggressive steroid therapies for proliferative ear disease; the consideration for systemic antimicrobial therapy (for proliferative ear canal disease); the potential for tympanum perforation which dictates the type of topical otics that should be used in the ear (products less likely to be ototoxic if concerned about perforation).

**Cytology** - should be performed at the initial visit and at every recheck for patients with otitis externa, until the ears are normalized. When pathology is involving the ear canals, samples are collected by passing a cotton tipped swab down in the ear canal to the junction of the horizontal and vertical canals (point at which the swab usually naturally stops). It is rubbed along the walls of the vertical canal and over the entrance to the vertical canal and adjacent parts of the medial pinna. If the better part of the medial pinna is involved, samples can be obtained by swab or by acetate tape impression (drop of “blue” stain from the Diff Quick series of stains placed on a slide, then the acetate tape placed over this; slide placed between a paper towel and excess stain “squeezed” from preparation). Morphologically describe bacteria (diplococci are generally staphylococcal spp.; rods are usually gram negative bacteria) and count bacteria, yeast, inflammatory cells (e.g. use 0 to 4+ scale so can roughly compare numbers from visit to visit). Cytologic results are mandatory for the diagnosis of secondary infections. The nature of wax and “smell” of the ears (e.g. suggesting secondary Malassezia) have been shown to be very inaccurate for the purpose of diagnosing secondary infections. These results help to dictate the choice of topical medication used in the treatment of the secondary infection. Other interpretations:

1. If bacteria persist in the face of therapy - resistance? Poor owner compliance regarding therapy?
2. If clinical evidence of otitis persists with no bacteria/yeast present - allergies, ceruminous otitis? Use your history and physical examination to better establish which may best apply.
3. Neutrophils present where neutrophils were not part of the original cytology may suggest a contact reaction or irritation produced by a topical medication.
4. Cytology is noted to be more accurate in identifying Malassezia than culture.

**Culture and Sensitivity (C/S) Testing**: There is a great deal of controversy regarding the use of culture and sensitivity testing in choosing appropriate therapies for otic infections. The correlation between C/S results and response to topical therapy is not very good. This likely has to do with the
fact that when resistance is noted on sensitivity testing, the cut offs used for differentiating sensitive vs resistant are based on blood/tissue concentrations that are achieved with parenteral administration (microgram/ml concentrations of the antibiotic). Topical antibiotics are routinely used at mg/ml concentrations which are 100 to 1000 times above these concentrations. These higher concentrations may prove efficacious, even when resistance has been reported to the lower concentrations of antibiotic. It is for this reason that initial selection of antibiotic therapy for bacterial problems is often made on the basis of cytology. C/S testing is done in the following scenarios:

1. Secondary bacterial infections have been treated with several antibiotics in the past and the bacterial problem is persisting.
2. Resistant strains of bacteria are suspected because bacteria are persisting on cytologic examination in the face of empiric antibiotic therapy.
3. In the presence of proliferative ear disease, C/S testing is used to choose an appropriate systemic antibiotic. The concentration of antibiotic achieved within the lining of the ear canal should exceed the MIC established for that bacteria within the tissues (i.e. the bacteria should be sensitive to the antibiotic).

It is important to recall that otic cytology is more accurate for defining the presence of Malassezia in the ear than is culture. In that we rarely see anti-fungal resistance, sensitivities are also rarely required (and often difficult and expensive to obtain).

**Imaging**

Radiographs/CT/MRI are primarily done to diagnose and provide prognostic information regarding otitis media/interna in both the dog and cat. They will provide documentation of the presence and extent of calcification/ossification of the auricular cartilages and peri-auricular cartilage soft tissues. Because ossification is permanent, this may help in establishing the prognosis of severely stenotic, proliferative ear disease. If the ear canals cannot be “opened up” by shrinking the proliferative soft tissues with aggressive glucocorticoid therapy in severely ossified ears, it is often the ossification that precludes this response. Because ossification is permanent, such ears are best dealt with surgically (total ear canal ablation and lateral bulla osteotomy).

**Diagnostic Techniques for Otitis Media**

**Direct Examination of the Tympanum:**

If the patient has otitis externa and the tympanic membrane is perforated, it is assumed that the patient also has otitis media due to the extension of debris/infection from the canal. If further diagnostics (sampling from the middle ear for cytology and C/S) and therapies (e.g. deep ear cleaning) are not possible, then anti-microbial treatment is established empirically, based on cytologic findings from the canals (topical and systemic antibiotic/antifungal therapy). In situations wherein debris is covering the tympanic membrane and it cannot be grossly evaluated, a higher index of suspicion for perforation (and the presence of otitis media) is noted if:
1. It is a very severe otitis (severe inflammation, erosion ulceration; seropurulent to greenish, slimy exudate; “rods” seen on cytologically. These changes all suggest a secondary Pseudomonas infection. Pseudomonas is noted to produce various enzymes that are capable of breaking down the tympanum; there is a higher incidence of perforation associated with these infections.

2. There are neurologic signs of otitis media (Horner’s syndrome, facial paresis or paralysis, KCS or xeromycteria (lack of nasal secretions) producing a dry nose on the affected side and/or signs of concurrent otitis interna (inner ear disease - head tilt, asymmetric ataxia, horizontal nystagmus - peripheral vestibular signs

A higher index of suspicion of an otitis media is associated with a tympanum that is intact but abnormal (more opaque, thickened, discolored, neovascularized; pars flaccida may be dilated and exudate/fluid/debris filled). In most cases, this is due to otitis media related to ascending infection or fluid accumulation within the middle ear due to auditory tube dysfunction. However, it is also possible to have an otitis media develop via a perforated tympanum (otitis externa) and have the tympanum heal over an active otitis media. The tympanum in these cases is usually abnormal (ore opaque, thickened, discolored, neovascularized). This appears to happen most commonly with proliferative ear canal disease. This has to be differentiated from situations wherein the tympanum becomes more opaque, whitish in color and thickens because waxy debris has been sitting on its surface for prolonged periods of time (months or years).

**Imaging**

Different diagnostic imaging modalities do have various capabilities with respect to defining the presence of middle ear disease. The “gold standard” would be CT scan. This is very sensitive and specific for the presence of otitis media. It can also be used to differentiate those situations in which debris has pushed the tympanum in to the middle ear, but has not perforated the tympanum (the so called “false” middle ear). It may produce prognostic information. Lytic changes of the bulla or petrous temporal bone suggest the presence of bacterial osteomyelitis. When this is more severe, it carries with it a poorer prognosis for medical management of the otitis media. Lysis may also suggest neoplasia. Dilatation of the bony bulla along with lysis and proliferation suggests the presence of cholesteatoma (very poor prognosis for medical management). Contrast enhancement can be used to better assess soft tissue involvement. Ossification of the canals is readily evident. MRI is not as good for imaging the ear canals and bony middle/inner ear, but is useful for imaging soft tissue structures such as neoplasia, infection and nerves in or around the ears. In the dog, radiographs have a higher “failure” rate than CT (missing as many as 25% of cases with otitis media, especially more acute cases of otitis media; less severe otitis media). Radiograph views used include dorsoventral, right and left lateral obliques and rostroventral-caudodorsal open mouth (best view for evaluation of the bullae). Caution should be exercised in making sure false positive diagnoses are not obtained by miss-interpreting overlying densities. CT or radiographs are best done before any “deep” ear
cleaning is performed. This minimizes the chances that iatrogenic damage to the TM and the getting of fluid or debris in to the middle ear will be mis-diagnosed as a “real” otitis media. The sensitivity of radiographs for documenting middle ear disease in cats is better than for dog. Views used are as for the dog.

**Culture and Sensitivity Testing**

In association with any deep ear cleaning in a patient with a perforated tympanum, at the initiation of the deep ear cleaning (before the cleaning is started), a polypropylene catheter is used to obtain samples for cytology and culture and sensitivity testing from deep within the horizontal canal. Samples are then obtained from within the middle ear. Both the canals and middle ears are sampled because the populations of bacteria may differ. It has also been noted that the sensitivity pattern of a given bacteria (e.g. Pseudomonas) may differ from the canals and the middle ear. These samples are generally combined for purposes of culture and sensitivity testing.

**Myringotomy** - this procedure is recommended in those instances wherein there is a high index of suspicion for otitis media (material within the middle ear as seen on radiographs, CT or MRI; neurologic signs suggesting otitis media/interna; dilated, abnormal pars tensa; abnormal pars tensa) and the tympanum is intact. It is very important to again note that, after a deep ear cleaning, it is very common to see the pars tensa become abnormally thickened and opaque because of the debris that has been sitting on its surface for a long period of time. Finding this abnormality is not considered a strong enough rational for routinely doing a myringotomy to look for otitis media. A myringotomy is performed once the horizontal canal has been thoroughly cleaned and dried. We use either a 22 guage, 6 inch spinal needle attached to a syringe or a 5 F polypropylene catheter whose tip has been cut to a sharp angle to facilitate perforation of the tympanum. The myringotomy site is in the caudoventral aspect of the pars tensa, just above the floor of the horizontal canal. The needle/catheter is advanced until the tip hits bone. Aspiration is performed at that time. Samples are saved for cytology and culture and sensitivity testing.
Management of otitis externa: choosing the right topical and systemic treatments for otitis externa

Rod A.W. Rosychuk, DVM, DACVIM

Colorado State University, Ft. Collins, Colorado

The successful management of otitis externa relies heavily on the results of a thorough otoscopic and cytologic examination and recognition of the primary factor/s that had initiated the otitis. In general, the management of an acute “flare” of otitis involves ear cleaning, the resolution of secondary infections, the resolution of inflammation and, where possible, resolution or control of primary (causative) factors. In 85% of cases, these ends can be achieved with only topical therapy. Emphasis is placed on re-examination to assess endpoint of therapy. Special therapeutic considerations are given to the management of chronic, proliferative otitis, recurrent otitis externa (often allergic otitis), and otitis involving multi-drug resistant bacteria (e.g. Pseudomonas spp).

ACUTE OTITIS EXTERNA

Acute “flares” of otitis are most commonly allergy related, with either secondary Malassezia and/or Staphylococci (coccii) overgrowth/infection. Therapeutic courses for these scenarios, utilizing the following combination of products (ear cleanser and topical antibiotic/antifungal/corticosteroid) are generally 1-4 weeks in duration. Ideally cases are re-evaluated every 2 weeks until remission has been achieved. In choosing topical products for the management of acute otitis externa, there is usually a lesser concern for the potential of ototoxicity because the incidence of tympanum perforation in these scenarios is low.

Ear Cleaning

A clean ear should ideally be achieved in the management of every case of otitis externa. Accumulated ceruminous debris may prevent medication from coming in contact with the affected areas of the ear, may produce a microenvironment conducive to secondary infection; may be a nidus for infection, may inactivate ingredients (e.g. polymyxin B) and may directly irritate the lining of the ear canal.

Ear Cleansers (Cleanser/dryers; Ear flushes): In general, these products contain ceruminolytics (e.g. docusate sodium or diocyt sodium sulfoisuccinate, propylene glycol), antimicrobials (chlorhexidine, acetic acid, boric acid, salicylic acid etc.), ingredients that potentiate the antimicrobial effect of other ingredients (TrisEDTA which potentiates the effects antibiotics and chlorhexidine) and/or drying agents (isopropyl alcohol etc.).

Although studies have been done to compare ceruminolytic activity of some of these products, they have all been done “in vitro”, utilizing a mixture of lipids designed to mimic natural canine ear wax. Their applicability to “in vivo” situations is really not known. Most of our knowledge regarding “which cleanser to use in what situation” is largely anecdotal. To meet the needs of the majority of cases seen in practice, we would recommend having at least two types of cleansers with various
ceruminolytic potential: one for more exudative ears and two with various degrees of ceruminolytic activity for various degrees of waxy accumulations.

Most ear cleansers contain ingredients with anti-microbial potential. We do know that secondary infections can be resolved with the aggressive use of these cleansers. For instance, ear cleaning twice daily was noted to significantly decrease signs of otitis and resolved secondary infections in 68% of ears treated with EpiOtic Advanced (Virbac). Although effective as an antimicrobial, this frequency of cleaning/“flushing” is often not tolerated well by dogs and for this reason, cleansers are often used as adjunctive antimicrobial agents (along with other topical antibiotic/antifungal products).

Cleanser “groups”, based on ceruminolytic and antimicrobial profiles. Several examples are given in each group because these products are variably available throughout the world. We would recommend stocking one from each group. There are some that you might not stock, but obtain for only more specific scenarios (listed at the end):

Good “all around” cleansers with good ceruminolytic activity (for moderate to severe wax accumulation) and antimicrobial activity:

1. Duoxo Micellar solution (Ceva/Sogeval) - phytosphingosine .02%, denatured alcohol, polysorbate 80, propylene glycol, laureth 9., polaxamer 184, biosaccharide gum 2, imidazolidinyl urea (good cleanser; drier wax; lesser antimicrobial activity; appears to be safe in the middle ear.
2. Epi-Otic Advanced (Virbac): Salicylic acid 0.2%, disodium EDTA, docusate sodium, PCMX, monosaccharide complex (l-rhamnose, d-galactose, d-mannose) (good cleanser; good antimicrobial activity; ototoxicity potential - author does not use if perforated TM).
3. Oti-Clens (Zoetis) - propylene glycol, malic acid, benzoic acid, salicylic acid, simethicone - potentially ototoxic
4. OtiRinse (Bayer) - propylene glycol, SD alcohol, dioctyl sodium sulfosuccinate, glycerin, nonoxynol-12, salicylic acid, lactic acid, benzoic acid, benzoyl alcohol, aloe vera - potentially ototoxic
5. Otoclean (Laboratories Dr. Esteve SA, Spain; similar products available from other sources in Canada and Europe) salicylic acid, lactic acid, oleic acid, propylene glycol, sodium lauryl sulphate, glycerin, plant extracts. Performed very well as a ceruminolytic in in vitro studies,2,3 potentially ototoxic

Cleansers for more exudative ears; good antimicrobial effects; weaker ceruminolytic activity

1. Mal-A-Ket Plus TrisEDTA ear flush (Dechra) - .15% chlorhexidine, .15% ketoconazole, TrisEDTA, ketoconazole (good antimicrobial potential; milder cleanser potential; potentiates the effect of antibiotics that are subsequently placed in the ear because of the TrisEDTA; safe in middle ear).
2. Malacetic Otic (Dechra) - 2% acetic acid, 2% boric acid, glycerin, polysorbate, triethanolamine (good anti-microbial - especially Malassezia effects; milder cleanser). Potentially ototoxic.
Others:

1. Klear Otic (Dechra) - 22% squalene, isopropyl myrisate, mineral oil; Cerumen (Vetoquinol) - 25% in isopropyl myrisate-liquid petrolatum: especially for drier wax accumulations. Product tends to leave more residual oil; very messy. Safe in the middle ear.

2. Tris EDTA containing products - several of these are used as “pretreatments” prior to instilling antibiotics in the ear. As a “pretreatment” they may then also function as a cleanser. TrisEDTA is a chelating agent. It chelates metal ions in bacterial cell walls, increasing permeability to various antibiotics (e.g. amikacin, neomycin, gentamicin, marbofloxacin, enrofloxacin) and antimicrobials (chlorhexidine), enhancing susceptibility these other ingredients. It is often used in the ear prior to placing the topical antibiotic in the ear. Used in this fashion, it is actually used as a cleaner. Some of these products may be combined with a surfactant to enhance cleaning ability. Products: Mal-A-Ket plus TrisEDTA (Dechra); TrizEDTA (just TrisEDTA; Dechra); TrizUltra + keto (trizEDTA and .15% ketoconazole; Dechra); T8 solution (benzyl alcohol, nonoxynol 12, PPG-12/PEG-50, lanolin TrisEDTA, Bayer) and T8 Keto (.1% ketoconazole, surfactants, benzyl alcohol, TrisEDTA; Bayer); Otodine (VioVet; lactic acid, TrisEDTA, chlorhexidine).

3. N-acetyl-cysteine (20%) - diluted to 2%; used as a “pre” treatment to clean the ear; 30 minutes prior to placing an anti-biotic containing product in the ear. This therapy is primarily considered when exudates are more “slimy”; suggestive of biofilm.

4. White vinegar and water (5 % acetic acid; diluted 1:2 to 1:3 in water). Reasonably good germicidal activity (especially pseudomonas; yeast); less effective cleanser; safe in middle ear.

Cleansing techniques

1. “In clinic” cleaning on awake animals:
   a. Ear bulb syringe - ideally place ceruminolytic in ears 15-20 minutes before flushing.

2. At home cleansing (flushing)- use of cleanser (e.g. Mal-A-Ket plus TrisEDTA): for mild to moderate amounts of wax - once every other day flushing; for moderate to severe wax accumulation, once daily. “No rush to the flush” - i.e. dogs and cats often do not like having their ears flushed. Consider starting topical anti-inflammatory/anti-microbial therapy for 2-4 days to “quiet” the ears down, then start flushing. Fill ear until overflowing; gently massage; allow dog or cat to shake material out. Can use a cotton ball to “soak up” debris and clean medial pinna of ear. In most instances, other medications can be placed in ear right after flushing although it is best to separate these times by an hour or so.

“First Line” Topical therapies for Otitis Externa

The vast majority of products marketed for the treatment of otitis externa contain an antibiotic, anti-fungal and glucocorticoid.

The antibiotics chosen for inclusion are generally those that have known efficacy for treating staphylococcus spp. (the most common bacteria associated with OE) and to a lesser degree gram
negative bacteria (specifically *Pseudomonas* spp.). Newer products have tended to include antibiotics that may have greater efficacy for treating gram negative bacteria (specifically *Pseudomonas* spp.). “First Line” antibiotics include: neomycin (good gram positive spectrum; does not cover pseudomonas); gentamicin (excellent gram positive spectrum; 50-60% of *Pseudomonas*), framycetin (neomycin B; good gram positive spectrum; poor for pseudomonas; good for other gram negatives); fucidic acid (fucidin; good gram positive spectrum); Polymixin B (good gram positive spectrum; good anti-*Pseudomonal* effects - but may vary with formulation; inactivated in purulent debris). Although fluoroquinolone containing products are considered by some to be “first line” antibiotics, the author would position them as “second line” (indicated by the finding of “rod” shaped bacteria predominating on cytology that suggest *Pseudomonas* or based on the results of culture and sensitivity testing). These include marbofloxacin, enrofloxacin, orbifloxacin (excellent gram positive spectrum; some anti-*Pseudomonal* effects - listed in relative decreasing order of efficacy for *Pseudomonas*).

The anti-fungals associated with these products in general have good anti-*Malassezia* effects. Although comparison of efficacy is controversial, a listing of relative efficacy, from most to least might be posaconazole, clotrimazole, ketoconazole, miconazole, nystatin, thiabendazole, silver sulfadiazine.

Glucocorticoids decrease the pain, inflammation (dermal thickening and stenosis) and wax production (by decreasing sebaceous and ceruminous gland activity) associated with otitis. The potency of the topical glucocorticoids included in these products is also somewhat controversial. They may be affected by the vehicles they are in. A listing in decreasing order of relative potency might be: fluocinolone, mometasone furoate, betamethasone, dexamethasone, hydrocortisone aceponate, triamcinolone, prednisolone, hydrocortisone.

More commonly used “combination” products:

1. Otomax (Merck; gentamicin, betamethasone, clotrimazole) - BID to start.
2. Mometamax (Merck; gentamicin, .1% mometasone furoate monohydrate, clotrimazole) - contains a longer acting and more potent, soft steroid that is minimally absorbed - mometasone. Once daily to start.
3. EasOtic Suspension (Virbac; gentamicin sulfate, miconazole, .11% hydrocortisone aceponate - a soft steroid; minimally absorbed).
4. Surolan - (Elanco; Polymixin B, miconazole, .5% prednisolone); polymixin and miconazole shown to be synergistic for *Pseudomonas* in vitro; BID therapy to start.
5. Tresaderm - (Merial; neomycin sulfate, dexamethasone, thiabendazole, propylene glycol) - BID therapy to start. Higher incidence of reactions to topical applications, because of neomycin and propylene glycol.
6. Panalog - (Zoetis; neomycin, triamcinolone acetonide, nystatin); other products that have a similar make-up; marketed in various parts of the world - Animax, Oribiotic, Oridermyl; BID to start.
7. Canaural (framycetin/fucidin, nystatin, .25% prednisolone)
8. Dexoryl (gentamicin, thiabendazole, dexamethasone)
9. Gentocin Otic (gentamicin, 0.1% betamethasone; solution)
10. Posatex (Merck; orbifloxacin, posaconazole, mometasone) - Product most commonly used in our clinic for Malassezia that appear to be resistant to other topical anti-fungals. Once daily therapy.
11. Aurizon (marbofloxacin, clotrimazole, 0.1% dexamethasone)

These “combination” products are generally used either once or twice daily to initiate therapy. Amount used is dictated by the size of ear. Small ears (cat, small dog) - 3-4 drops; medium sized dogs (Golden retriever) - 6-8 drops; large dogs (St. Bernard) 12-16 drops. When medicating the ears, the tendency on the part of owners is to not use enough medication. In part, this may be related to the necessity of counting “drops”. Consideration can be given to placing the medication in a multi-dose vial and providing the owners with a syringe to more accurately measure recommended amounts of medication. Attention should also be paid to the inner aspect of the pinna, if involved. This area also has a tendency to be “under treated” by owners.

It should be noted that virtually all of the above products are not indicated for use in association with the presence of a perforated tympanum (concern for ototoxicity). The author has seen several cases of ototoxicity (hearing loss) associated with Otomax, Mometamax, Panalog and Tresaderm. This is in part related to the fact that these are the products most commonly used in our clinical practice area. Interestingly, on a rare occasion, ototoxicity has been seen with an proven intact tympanum (specifically with Otomax and Mometamax).

Products for Special Indications:

Only Malassezia seen cytologically - ideally use a product that contains only an anti-fungal and glucocorticoid; does not contain an antibiotic. There are unfortunately no good commercial options that meet this ingredient profile. For this reason, we commonly use a topical “mix” made in our pharmacy - combination of 1% miconazole (spray) and injectable dexamethasone sodium phosphate (4 mg/ml); most common ratio is 1:1, but can change the ratio as necessary - i.e. if want more anti-inflammatory effect, 1 part miconazole to 2 parts dex. Because this is an aqueous product, we tend to use larger volumes of solution for each treatment - i.e. for medium sized dogs - 0.5 - 0.8 ml, small dogs and cats - 0.3 - 0.4 ml; large breed dogs - 0.8 - 1.2 ml. Treatment is usually started on a BID basis.

“Long Duration of effect” Topical Therapies: These products require that the ear be cleaned and dried prior to the administration of the product. They continue to exert their beneficial effects over prolonged periods (weeks). Between treatments, ear cleansers cannot be used. The commercial products marketed for this purpose are indicated for the treatment of Staphylococcal sp. and Malassezia. They include:
1. Osurnia (Elanco; gel; 10 mg florfenicol, 10 mg terbinafine, 1% betamethasone) - every 7 days for two treatments; effects may last for as long as 45 days. Recommended that the ear not be cleaned for 45 days.

2. Claro (Bayer; 16.6 mg florfenicol, 14.8 mg terbinafine, 2.2 mg/ml mometasone furoate). Duration of effect is 30 days after initial application. The ear should not be cleaned during this time.

In a recent publication looking at dogs with acute otitis externa (≤ 2 weeks), dogs with ears initially cleaned with a ceruminolitic, then treated by a Veterinarian with two consecutive weeks of Osurnia were compared to those wherein owners treated with Posatex daily and twice weekly ear cleaning with a ceruminolitic. Ears were examined on days 0, 7, 14 and 28. There was no difference in improvement between groups at any time point, although cytology scores and pruritus improved significantly more by Day 7 in the Osurnia treated ears. Quality of life assessments for the owners were significantly better for the Osurnia treated group 5. In our hands, these products, while efficacious, do appear to have a higher failure rate than several other “conventional” cleanser/topical treatments, in part due to its restricted spectrum of antimicrobial coverage, failure to adequately clean the ears at the initiation of therapy and debris re-accumulation noted during therapy. That said, they are effective therapies. In our clinic they are not used as a “first” line therapy for treating otitis externa. They are primarily used for dogs who are otherwise difficult to treat or for clients who simply cannot provide the frequency of topical treatments required of “conventional” cleanser/topical treatment regimens.

Other products with extended durations of effect:

1. Poloxamers (liquid at refrigerator and room temperatures; solidifies at body temperature in ear). Contents slowly released. Can have made up by formulating pharmacy to have various ingredients chloramphenicol, ketoconazole, betamethasone OR enrofloxacin, ketoconazole, triamcinolone OR amikacin, ketoconazole, triamcinolone OR gentamicin, ketoconazole, triamcinolone OR mupirocin, ketoconazole, triamcinolone. Duration of effect - 7 days.

Systemic Antimicrobial Therapy

The efficacy of the use of systemic antibiotic therapy in the management of otitis externa is controversial. There are very few reports regarding the use of systemic antibiotics in treating bacterial otitis externa. Studies looking at the oral dosages of antibiotic that would be required in order to exceed the MIC of *Pseudomonas* spp. and *staphylococcus* spp. in otitis suggest that they are higher than for cutaneous infections (e.g. at least 5 mg/kg/day for marbofloxacin). Clinical efficacy has not been well documented. At this time, we recommend systemic antibiotics when bacteria are seen in the ear and the otitis is proliferative; when the otitis is severe (usually ulcerative) and large numbers of neutrophils are noted on cytologic examination (suggests a deeper infection); in treating otitis media; when owners cannot administer topical therapy. Antibiotics are best chosen by culture and sensitivity testing but empiric choices include a cephalosporin when cocci are seen cytologically or
marbofloxacin if “rods” are seen cytologically. There is again very little data regarding the efficacy of systemic anti-fungal therapy in treating otitis associated with malassezia. In one study, only partial responses were noted to systemic therapy, suggesting that both topical and systemic therapy would be required for resolution. This has mimicked our clinical experience. We recommend a systemic anti-fungal for proliferative otitis, for otitis media and when owners are unable to treat topically when Malassezia is involved. Therapeutic options: ketoconazole - 5 mg/kg q 12-24 hours;itraconazole - 5 mg/kg q 24 hrs or pulse dosed 2 days on and 5 days off.

**Systemic Glucocorticoids**

Systemic glucocorticoids will rapidly reduce edema, swelling and pain associated with acute otitis externa, no matter what the cause (although most effective for allergic otitis); they are perhaps the most effective therapy for reducing hyperplastic changes, although this will happen more slowly. For acute otitis externa, we generally start therapy with oral prednisone/prednisolone at 0.5 to 1.0 mg/kg/day (use higher range for more severe inflammatory changes); 2 week tapering dosage. For proliferative ears, see below.

**Client Education and Follow-up**

It is very important to provide both proper instructions for medication use and to provide the client with instructions to take home (e.g. medication application technique, frequencies, amounts etc.). For difficult to medicate dogs or cats, the owner may try placing the appropriate number of drops for a given treatment in a syringe (e.g. tuberculin) then rapidly squirting this in the ear.

Follow-up: the initial recheck for most cases of otitis externa is usually done two weeks after initiating therapy. Subsequent rechecks are dictated by response to therapy. Each follow-up examination should involve an otoscopic examination, cytologic examination of exudates and an accurate recording of findings. Routine rechecks should be maintained until the problem is either resolved or controlled.

**CHRONIC MANAGEMENT OF ALLERGIC OTITIS EXTERNA**

The most effective systemic therapy for the management of atopic otitis does appear to be oral glucocorticoids. Steroid alternatives that appear to be of little or no apparent value in this regard include fatty acids and antihistamines. Apoquel® (oclacitinib; Zoetis), Cytopoint® (Canine Atopic Dermatitis Immunotherapeutic; Zoetis) and Atopica® (cyclosporine) in general do not perform as well for controlling atopic otitis as they do for the more generalized signs of atopic dermatitis. Although we do see some atopic otitis cases benefit from Apoquel® therapy, for a greater percent of our patients, this is not the case. Individuals on Apoquel® often remain prone to “flares” of secondary Malassezia/bacterial infections. These “flares” appear to be related to the fact that significant inflammation persists within the ears, in spite of the Apoquel® therapy. Atopica (cyclosporine) may be somewhat more effective for the long term management of proliferative otitis, especially in the Cocker Spaniel.
Immunotherapy also appears to produce variable beneficial effects with respect to otitis control. It is also not uncommon to have to use long term, topical otic maintenance therapy in individuals on immunotherapy to maximize otitis control.

In the author’s experience, the most beneficial long term topical otic therapy for otitis is a glucocorticoid. Although the use of ear cleansers/flushes with their antimicrobial activity and ability to facilitate wax removal can be of benefit, inflammation often persists within the ears and affected individuals may remain prone to “flares” of otitis (+/- secondary infections). Control of allergy related inflammation with a topical glucocorticoid often does a better job of controlling such “flares”. The benefits of such therapy have been supported by a study looking at the use of a once weekly ear cleanser compared to 3 drops of Cortavance® (hydrocortisone aceponate; Virbac) in the ears for two consecutive days of the week. Over 6 months, 95% of the Cortavance® treated ears were free of relapse; 50% for the ear cleanser treated ears.

Long Term Management Scenarios:
1. A topical glucocorticoid/ear flush regimen may be adequate for treating allergic otitis externa, without any other systemic therapy for allergy, especially if the ears are the predominant source of allergy related problems.
2. As an adjunct therapy to any one of the systemic therapies noted above for allergy control (e.g. Apoquel).

Long Term, “Maintenance” Management Options:
1. Resolve all secondary infections; remove debris - with conventional therapies
2. Routine use of a “flush” such as Mal-A-Ket® Plus (Dechra) or Douxo Micellar® solution (Sogeval) on a once or twice weekly basis. These products help to take over for the natural flushing mechanism of the ear (lateral epithelial migration) that is often no longer functional in allergic ears. They also have some anti-microbial effects and help reduce the tendency towards the development of secondary bacterial and yeast infections.
3. Long term therapy with a topical glucocorticoid:
   a. 1:1 mix of dexamethasone sodium phosphate and 1% miconazole - if prone to secondary Malassezia. Some individuals with more severely inflamed ears will benefit from a higher concentration of dexamethasone (a 2 part dex. to 1 par miconazole) dilution. Usually used once or twice weekly for maintenance (most commonly twice weekly).
   b. 1:1 to 2:1 mix of dexamethasone sodium phosphate in saline; if not prone to secondary infections. Once or twice weekly (most commonly twice weekly).
   c. Cortavance (Virbac) - .15 - .25 ml twice weekly
   d. Less severely, inflamed ears: CortAstrin® (1% hydrocortisone; aluminum acetate astringent) - once every 48-72 hours long term
“SAFER” TOPICAL THERAPIES WHEN THERE IS CONCERN FOR OTOTOXICITY

The use of topical medications in an ear with a perforated tympanum must be approached with caution. Medication may move from the middle ear to the inner ear to affect cochlear or vestibular function. Hearing loss is the most commonly encountered ototoxicity. Factors that are noted to enhance ototoxicity problems include length of drug administration, dose, the presence of pre-existing cochlear or vestibular disease, health status of the patient and genetic predispositions. In most cases of more acute otitis externa (weeks of involvement), the tympanum is usually intact, even though the ear may be filled with debris. In these cases, topical therapy can usually be chosen without concern for the integrity of the tympanum. In the dog, signs that should make one more concerned about the presence of a perforated tympanum, when the TM cannot be evaluated (debris; stenosis) would include: neurologic signs of otitis media/interna; severe stenosis of the horizontal canal due to chronic proliferative changes; severe (may be acute) purulent otitis externa - “rods” (usually indicative of Pseudomonas) seen on cytologic examination. Pseudomonas produces proteases that are capable of breaking down tympana. In cats, if the TM is not visible because of debris accumulation, even with an “acute” flare of otitis, we tend to use “safer” topicals. The other guidelines as listed above for the dog also apply, although it is uncommon for us to see both proliferative canal disease and secondary pseudomonas otic infections in cats.

Topical drugs noted to be potentially ototoxic that should be avoided when perforation of the tympanum is known or expected include: neomycin; gentamicin (when in commercial formulations such as Otomax or Mometamax), polymixin B, chloramphenicol propylene glycol.

In general, topical fluoroquinolones (enrofloxacin, marbofloxacin, ciprofloxacin), topical steroids (e.g. injectable dexamethasone sodium phosphate; fluocinolone and DMSO - Synotic, Zoetis) and topical antifungals (miconazole, clotrimazole, ketoconazole) appear to be well tolerated in the middle ear. Formulated “mixes” that are routinely used in our clinic when there is concern for potential perforation of the TM:

1. For bacteria: injectable enrofloxacin (22.7mg/ml): dexamethasone sodium phosphate (4 mg/ml) at a ratio of 1:2; when a more potent steroid effect is desired - 4 ml enrofloxacin (22.7 mg/ml) to 8 ml Synotic (fluocinolone and DMSO; 3-8 drops BID to start).
2. For Malassezia: dexamethasone sodium phosphate (4 mg/ml): 1% miconazole (1:1); if a more potent steroid effect is desired: Synotic and 1% miconazole - 1:1 (3-8 drops BID to start)

These aqueous enro./dex./micon. formulations are stable for at least one month.

Volumes used for the aqueous enro./dex.micon mixes: for small dogs and cats - 0.3 to 0.4 ml; medium sized dogs - 0.5 - 0.8 ml; large breed dogs - 0.8 - 1.2 ml). Therapies are usually started BID.
“Safer” ear flushes: Mal-A-Ket Plus (Dechra); Douxo Micellar Solution (Sogeval); dilute white vinegar and water (1:2 to 1:3)

THERAPY FOR PROLIFERATIVE OTITIS EXTERNA

In most instances, these are chronic allergic ears with secondary infections. Stenosis is variable and due to epithelial hyperplasia, dermal expansion (ceruminous gland dilatation and hyperplasia, sebaceous gland hyperplasia, edema, inflammatory cell infiltration and fibroplasia) and variable degrees of ossification of the auricular cartilages and surrounding soft tissue. Stenosis often precludes visualization of the TM (which, in many cases may not be intact). The basic tenants of “salvaging” cases of chronic, proliferative otitis externa: improve or resolve proliferative changes; resolve secondary infections; remove debris from the ears and resolve or control the underlying primary factor (most commonly atopy and/or food sensitivity). Initial emphasis is placed on “opening up” the canals of the ear (i.e. widening the lumen). A patent ear canal is considered essential to the effective medical management of all cases of chronic otitis externa.

Because of permanent changes within lining of the ear canals, once the above have been achieved, it is not uncommon for these individuals to require long term, topical maintenance management for their ears (cleanser; topical steroid).

Systemic therapy:

1. Systemic glucocorticoid: starting at 1-2 mg/kg/day prednisolone/prednisone for two weeks (2 mg/kg/day for severe proliferative changes), then 0.5-1 mg/kg/day for two weeks, then 1 mg/kg every other day for two weeks, then 1.0-0.5 mg/kg every other day for two weeks and gradually taper. Systemic glucocorticoid therapy is generally maintained until proliferative changes significantly reduced.

2. Oral cyclosporine - as a steroid alternative for reduction of proliferative changes associated with allergic disease, cyclosporine is only variably effective. Anecdotally, it would appear to be more effective in cocker spaniels with proliferative disease. Lower dose, concurrent steroid therapy can be used early in the course of the cyclosporine therapy, to hasten the response to treatment. Interestingly, for severe proliferative disease, it often takes more aggressive dosages to see benefit (5 mg/kg BID).

3. Systemic antibiotic (if bacteria present cytologically) - chosen on the basis of cytology initially - cephalexin for cocci, marbofloxacin or enrofloxacin for rods; ideally do culture and sensitivity testing and choose subsequent antibiotic therapy based on this data

4. Systemic anti-Malassezia therapy (if Malassezia present on cytology) - for dogs - ketoconazole at 5-10 mg/kg BID, terbinafine - 30 mg/kg/day, or itraconazole at 5 mg/kg q 24 hrs.
5. Restrictive diet trial - if food sensitivity is considered a possible primary factor for the problem. If this is indeed the case, then response to the above medications will often be enhanced by being on the diet. These diet trials are characteristically very long (often 3-4 months). In the earlier stages of the diet trial proliferative changes are minimized, secondary infections are resolved, debris is removed from the ear, then anti-inflammatory medications are gradually removed so that, towards the end of the diet trial, one has a better chance of assessing response to the diet alone.

Topical Antibiotic and/or Anti-Malassezia Therapy if The Integrity of the Tympanum is Unknown or the tympanum is known to be perforated (should not cause ototoxicity): See “Safer” topicals listed above.

Topical Potent Glucocorticoid - safe if tympanum not intact

Synotic® (Zoetis; fluocinolone and DMSO) - very potent steroid (100X potency of hydrocortisone) - 3-8 drops BID to initiate. If an antibiotic effect necessary, add enrofloxacin (22.7 mg/ml) - 2 parts Synotic: 1 part enro. OR, if an anti-Malassezia effect desired, Synotic: 1%miconazole (1:1).

Factors affecting the Prognosis of Chronic Proliferative Otitis Externa

For severely stenotic ears: if, after 3-4 weeks of aggressive oral and topical steroids, appreciable reduction in the stenosis of the canals is not noted, then the prognosis for the medical management of the problem is poor and consideration should be given to total ear canal ablation. This most commonly occurs in ears that are extensively ossified. If the owners are unable to medicate the ears well, then the prognosis for the successful long term medical management of the ears is poor.

TOPICAL THERAPEUTIC ALTERNATIVES FOR THE MANAGEMENT OF PSEUDOMONAS OTITIS:

1. Ideally initiate therapy with a thorough, deep ear cleaning to remove biofilm, exudates, wax, bacteria. This also allows for the assessment of the integrity of the tympanum (to help direct choices of topical therapy).

2. Glucocorticoids (both topically and systemically) are of very significant benefit. They help to normalize the otic environment, which in itself inhibits Pseudomonas growth. Oral prednisone/prednisolone starting at 0.5-1.0 mg/kg/day for 1-2 weeks, then 0.25-0.5 mg/kg/day for two weeks, then this dose every other day for two weeks. Start at the higher end of the dosage range with more severe inflammation. If significant proliferative disease (need to “open up” the ear canal, start at 1-2.0 mg/kg/day.

3. Cleansers of choice (usually once daily):
   a. TrisEDTA containing products: e.g. Mal-A-Ket plus, Dechra; TrizUltra plus ketoconazole, Dechra; intended to enhance the effect of antibiotics put in the ear
   b. 2% N acetylcysteine (for very “slimy” ears; suspicion of biofilm) - use as flush 30 minutes before putting antibiotic in ear (dilute 20% acetylcysteine to 2% with saline)
c. Acetic acid containing flush (e.g. Malacetic Otic, Dechra) or dilute white vinegar (5% acetic acid; dilute 1 part vinegar to 2 parts water; acetic acid has direct anti-pseudomonal effects)

4. Empiric choices of topical antimicrobial therapy (suspect Pseudomonas because see “rods” on cytology; nature of exudate etc.)

Tympanum intact:

a. Gentamicin containing products: Otomax (Merck), Mometamax (Merk), Gentocin Otic

b. Polymixin B containing products: Surolan (Elanco); Cortisoporin Otic solution (human product) - 1.6 mg/ml or 10,000 units/ml polymixin B, Glaxo Wellcome OR one ml ampule containing 200,000 units polymixin B - dilute with sterile water to 10,000 units. Note: because of their higher concentration of polymixin, the latter formulations may be more effective than available veterinary commercial products (Surolan).

c. Marbofloxacin containing product: Aurizon

Tympanum not intact or integrity of tympanum not known (safe in the middle ear):

a. Enrofloxacin containing products/preparations (* = those most commonly used by author); usually BID to initiate therapy
   i. enrofloxacin (22.7 mg/ml) + dexamethasone sodium phosphate (4 mg/ml) - 1:2; just bacteria*
   ii. enrofloxacin (22.7 mg/ml) plus 1% miconazole and dexamethasone sodium phosphate (1:2:1); bacteria and Malassezia*
   iii. Enrofloxacin (22.7 mg/ml) plus dexamethasone sp (4 mg/ml) plus TrisEDTA + ketoconazole (TrizUltra + ketoconazole - Dechra) (1:1:4)*
   iv. N acetyl cysteine (20%) - 6 mls, plus 6 mls of enrofloxacin (100 mg/ml) plus 100 ml TrisEDTA*.
   v. Baytril Otic (Bayer) – enrofloxacin and silver sulfadiazine (shown to be synergistic in vitro)
   vi. enrofloxacin (22.7 mg) plus saline 1:2 (no steroid)
   vii. enrofloxacin (22.7 mg/ml) plus Synotic - 1:2 (potent steroid effect; proliferative ears)
   viii. enrofloxacin (13 mls of 100 mg/ml injectable enrofloxacin) plus 118 ml of TrizUltra+ ketoconazole - Dechra)

5. Tympanum intact (because products ototoxic); based on culture and sensitivity testing:

a. Tobramycin - .3%; human ophthalmic solution or diluted (from 40 or 80 ml vials) to 8 mg/ml in saline or TrisEDTA. BID.

b. Ticarcillin or Ticarcillin and clavulonic acid The re-constituted product is suggested to have a shelf life of only 3 days at room temperature. It has been shown that the reconstituted product will retain its efficacy for one month at refrigeration temperatures (4 C). With this information in mind, the author now uses Timentin; 3.1 gm vial; reconstitute with 26 ml (100 mg/ml); placed in 4 ml aliquots in syringes and refrigerated. Each 4 ml aliquot is used over 2 days.
6. Tympanum not intact/treating otitis media/integrity of tympanum not known; chosen based on results of culture and sensitivity testing (not ototoxic) or sensitivity not available (silver sulfadiazine):
   a. Amikacin - 10-25 mg/ml in saline (250 mg/ml injectable diluted in saline) -.3 -.4 ml for small dogs; .5 -.8 mls for medium sized dogs; .8-1.2 ml for large breed dogs; BID to start.
   b. Amikacin (250 mg/ml) 3 mls amikacin + 14 mls dexamethasone sodium phosphate + 30 mls TrizEDTA (Dechra) or TrizUltra plus Keto. (Dechra) BID to start. We have used 10-15 mg/ml concentration in many middle ears with no obvious ototoxicity.
   c. Silver sulfadiazaine - empiric choice because sensitivity data not available: Silver sulfadiazine cream (safe in middle ear) - 1% cream diluted 1:9 with water (the Silvadene® product mixes well with water; generics may not). Another suggested mix: 1.5 ml of 1% SSD cream (e.g. Flamazine) in 13.5 ml water or saline. Can also make a 0.1% solution utilizing a SSD powder (usually compounding pharmacy). Ear should be cleaned prior to application to enhance efficacy. SID or BID to start.
   d. Ceftazidime:
      i. Dilute to 100 mg/ml; freeze in 4 ml aliquots to be used over two days. Start BID
      ii. 1 gram injectable solution with 24 mg dexamethasone in to 100 ml saline
Clinical manifestations of food allergy and practical management

Rod A.W. Rosychuk, DVM, DACVIM

Colorado State University, Ft. Collins, Colorado, USA

PATHOMECHANISM? Adverse reactions to foods are considered either food allergies or food intolerances. Although food allergies are considered most common, their true incidence remains unknown. Food allergies are immunologically mediated reactions to larger, water soluble glycoproteins that, in general, have molecular weights ranging from 10-60 kilodaltons (kDa). Potentially allergic proteins must be large enough to bridge at least two IgE molecules on the surface of mast cells to illicit degranulation and subsequent release of inflammatory mediators. Making these proteins smaller reduces this capability. However, it is important to note that even smaller sized particles (e.g. 3-5 kDa) may still be a problem. Food intolerances involve non immunologic mechanisms: idiosyncratic (e.g. sulfites or monosodium glutamate may stimulate the release of histamine from various cells); pharmacologic (vasoactive amines such as histamine are found in certain foods such as spoiled tuna, mackerel, skipjack and bonito). These intolerances have been documented in humans, and, although suspected to occur in dogs and cats, they have been only poorly documented in these species.

INCIDENCE?: The incidence of food allergy in dogs appears to vary throughout the world. Most recent publications, originating from Europe (Switzerland, Italy) and the eastern and southern United States suggest that 20-35% of nonseasonally allergic individuals (excluding flea bite hypersensitivity) are due to food sensitivity. In other parts of the world (France, Greece, Southwestern United States), the incidence is only 2-7%. At present, there is no good explanation for this difference. The concurrent presence of flea bit hypersensitivity and/or atopic dermatitis has been reported in 20-30% of cases and as high as 75% of cases.

ALLERGIC TO WHAT? In a recent evidence based study, summarizing data from around the world (Mueller RS et al, BMC Veterinary Research, 2016), the most likely food allergens contributing to canine adverse food reactions were, in decreasing order of incidence, beef, dairy products, chicken and wheat. Other glycoproteins that have been incriminated much less commonly include soy, corn, oatmeal, pasta, pork, lamb, fish, turkey, potatoes, rabbit, rice flour, rice, artificial food additives (gum carrageenan) and food preservatives. In one study of 25 food allergic dogs, 80% of affected dogs were reactive to 1 or 2 allergens in the diet. 64% were sensitive to two or more allergens. The mean number of allergens reacted to was 2.4.

CLINICAL MANIFESTATIONS: Nonseasonal pruritus is the most commonly encountered (because the offending component to the diet is consistently fed). In cases in which the offending food is fed sporadically, clinical signs may be intermittent. Pruritus is most commonly directed at the ears, perineum, distal limbs, axillae and groin. Any or all of these areas may be affected. Clinical lesions
are most commonly caused by self trauma and include alopecia, inflammation, hyperpigmentation, excoriations, ulceration and lichenification. The pruritus associated with food allergies are noted to be variably responsive to anti-inflammatory doses of steroid (i.e. 0.5-1.0 mg/kg prednisone/prednisolone). A small percentage of cases may be very steroid resistant. Primary eruptions (those that are not caused by self trauma) are possible and include erythematous wheals, papules, macules and plaques. Otitis externa is generally bilateral, but may be predominantly unilateral. Signs are restricted to only otitis externa in as many as 20% of all reported cases. These individuals will only have a non seasonal otitis (no more generalized pruritus). Other possible dermatologic signs include seborrhea (oleosa or sicca), acral lick dermatitis and acute pyotraumatic dermatitis. Affected individuals may be very prone to recurrent bacterial and Malassezia dermatitis and otitis externa. It is also possible to see recurrent bacterial pyoderma as the only sign of food allergy in the dog (no more generalized pruritus being noted). GI signs are noted in 5-30% of cases (incidence continuing to vary widely with the publication). GI signs are primarily vomition or diarrhea/soft stools. This may include the presence of fecal mucous, blood and tenesmus. Other signs such as increased numbers of bowel movements and flatulence and borborygmus have been anecdotally suggested to have a higher incidence in food allergic dogs, but this is controversial. The presence of GI signs in a patient with dermatologic signs suggestive of allergy simply heightens the possibility of food sensitivity.

Other rare clinical manifestations of food sensitivity include: perianal fistula, vasculitis, onychomadesis (nail plate sloughing), erythema multiforme, seizures and behavioral changes (depression, irritability) and respiratory signs.

**DIAGNOSIS:** The only diagnostic test that is effective for the diagnosis of adverse food reactions is the performance of a restrictive diet trial. While serum allergen specific testing (IgE), salivary allergen specific testing (IgA) and intradermal testing is available, there continues to be no validation for the use of these tests in diagnosing food sensitivity. They are not recommended.

**Restrictive Diets for Diet Trials (which is the best?)**

*Home prepared diets* appear to be closest to 100% effective in determining the presence of food sensitivity. There are several reports in the literature of both dogs and cats who have manifest signs of food sensitivity when fed a commercial diet consisting of the same ingredients offered in a home prepared form that the individual did not react to. Home prepared diets that the author favors include a single, novel carbohydrate (potato, sweet potato, yams [in the United States, what are labelled as yams are really sweet potatoes - soft variety], oats, squash, green peas or rutabagas; in all cases must be fresh - not instant or “minute packaged” cooking versions) combined with a single, novel protein (rabbit, ostrich, kangaroo, pinto bean). There is some data to suggest cross reactivity between venison and beef and various avian proteins (duck may cross react with chicken). In light of this, we have elected to avoid these novel proteins. We generally feed one cup per ten pounds
body weight of the mix per day; ½ of this mix is usually the protein component. It is not necessary to nutritionally balance these diets for the duration of a diet trial (8-12 weeks) in mature, healthy individuals. However, for long term use, the diet would have to be balanced. It is recognized that these diets are nutritionally inadequate for growth and maintenance. Homemade foods lack a source of calcium, essential fatty acids, certain vitamins and various micronutrients. These homemade diets are not recommended for trial purposes in growing animals unless they have been balanced with a non-flavored, additive free vitamin, calcium/phosphorous and a source of essential fatty acids such as vegetable oil. Vegetable oils are not likely to contribute to allergic symptoms. Recipes for balanced home prepared diets can be accessed through various sites: balanceit.com or you can go to the American College of Veterinary Nutrition website or through VIN (Clinical Nutrition Message Board). CSU has a nutrition service that will provide this support. Freshly prepared novel protein diets are available through raynenutrition.com.

Protein hydrolysates: it is known in man that major food allergens are typically large glycoproteins of molecular weight greater than 10-12 kDa. Hydrolysate diets have had their proteins broken down into smaller peptides which theoretically render them less allergenic. Most hydrolyzed diets contain both a hydrolyzed protein and an intact protein that is unlikely to be allergenic (most commonly corn starch). Examples include Purina HA (hydrolyzed soy protein, cornstarch), Hills Prescription diet z/d (hydrolyzed chicken liver and cornstarch), Royal Canin K9 Ultamino (chicken feather hydrolysate, corn starch, coconut/soy oil). Some data is available on the efficacy of these diets. In one study, 21 of 23 (90%) of proven food allergic dogs (allergens not specified) were noted to respond to the Purina HA diet. Similar success rates have been noted with Hill’s z/d. Data has been generated on the efficacy of some of these diets when fed to individuals known to be allergic to the protein in the diet. In one study (Beale DM Proceedings of the AAVD/ACVD, 2001), Purina Veterinary Diet HA Formula, which contains hydrolyzed soy and cornstarch was fed to 10 dogs with soy or corn sensitivities or both. Pruritus was reduced 50% in soy allergic dogs (n=6) and 80% in corn allergic dogs (n=4) compared to dogs fed intact soy or corn. Even in corn and soy sensitive individuals, pruritus and erythema could be expected to improve significantly on the diet, but not necessarily resolve (i.e. you may see a partial response). In another very recent crossover study (Bizikova P et al, Vet Dermatology 2016), Royal Canin Ultamino was compared to feeding Hill’s Prescrition diet z/d in 10 dogs with chicken induced adverse food reactions. Four of the dogs “flared” after being fed the z/d; none flared when fed the Ultamino. Why the difference between these diets? It likely has to do with the size of the hydrolyzed proteins. More than 99% of peptides found in the Ultamino product are below 6 kDa with the larger peptides originating mostly from chicory root fibre; 95% of the peptides originating from poultry feathers are below 1 kDa and 88% are single amino acids. In the z/d diet, 78% of the peptides are below 1 kDa, with approximately 7% ex exceeding 5 kDa. What is all this data trying to tell us about hydrolysate diets?
1. They would be expected to “define” most food sensitive individuals, recalling that the most common problematic proteins are beef, dairy products and wheat etc.

2. They may only partially improve or fail if fed to an individual who has a sensitivity to the protein hydrolysate in the diet (e.g. soy or chicken hydrolysate fed to an individual allergic to soy or chicken).

3. Because of the above, we quote a failure rate of 10-15% for these diets.

4. If you see a partial response to a hydrolysate diet, consider trying yet another restrictive diet trial (e.g. commercial novel protein or home prepared novel protein) to see if the remaining pruritus is due to food sensitivity vs atopy.

5. Of the hydrolysate diets, perhaps the diet of choice is the Royal Canin K9 Ultamino

Novel protein diets: e.g. Royal Canin duck, venison or rabbit and potato; kangaroo and oat; Hills Prescription Diet Canine d/d (rice and egg), Hills Prescription Diet canine d/d (Rice and Salmon; dry), Hills Prescription Diet Canine d/d (whitefish and rice; canned) etc. Primary questions related to the efficacy of these diets in better defining patients with food sensitivities are related to the possible cross reactivity of the novel proteins in some of these “restrictive” diets. For instance, it has been recently shown that there is cross reactivity between lamb and beef/cow’s milk. There is a suggestion that there may be cross reactivity between venison and beef and between duck and poultry. We do know that novel protein diets may fail to define some food sensitive individuals. We quote a failure rate of 10%. This is likely primarily related to cross reactivity of proteins in the diets. At present, the commercial novel protein diets that are used most commonly at Colorado State University include Royal Canin Kangaroo and oat and rabbit and potato.

Why not “over the counter” novel protein diets (i.e. those that are not veterinary prescription diets)? It has now been shown in several studies that potentially allergenic proteins are included in these diets, but not reported on the label. In three separate studies of both therapeutic and regular pet foods examined for species specific DNA, 14 of 17, 20 of 52 and 4 of 4 were miss-labelled. Soy was found in 3 of 4 “soy free” diets.

So…which diet should one choose for a restrictive diet trial? A diet history should be taken to establish the dietary ingredients that the patient has been exposed to in the past (especially the proteins in the diet). Although a home prepared diet may be ideal to initiate the trial, because of the difficulty obtaining the ingredients and preparing these diets (especially for larger breed dogs), a commercial restrictive diet is often the diet of choice. At this time, the answer to the question, “which is the best commercial restrictive diet” remains open for debate. It would appear that there is no commercial restrictive diet that will work for all food sensitive individuals. The failure rate may be slightly higher with certain hydrolysates (our anecdotal observation). With this in mind, we tend to initiate our elimination diet trials with a novel protein diet (most commonly RC kangaroo and oat, rabbit
and potato). When the diet history includes potato or oats or the diet history is not available (i.e. we are not sure what an individual has eaten in the past), we would go to a hydrolysate (RC Ultamino).

If a patient has failed to benefit from a commercial restrictive diet trial, our working diagnosis for the problem, by rule out, is usually environmental allergy. However, we recognize that a given commercial restrictive diet trial may not totally rule out a food sensitivity component to the problem. If diagnostics or therapies for environmental allergy do not appear to be benefiting the skin disease, then consideration should be given to “re-visiting” food sensitivity by trying a home prepared restrictive diet to better rule out a food sensitivity component to the problem.

Commercial elimination diets that can be used for growing dogs include Nestle-Purina HA canine, Royal Canin Hypoallergenic Canine.

What can be used as treats/chews/for giving medications?
1. Cooked potato, sweet potato, yams (which, in the United States are labelled as yams but are usually soft sweet potatoes).
2. Serenegy: Potato pleaser treats; Hopping oat treats; Potato WrapIt (must rehydrate; makes a dough consistency); Oats WrapIt.
3. Ostrich tendons, bones; Kangaroo bones; body parts - e.g. North Coast Pets. Multiple on line sources for sweet potato and yam dog chews.

**Diet Trial**

Transition to the restrictive diet slowly over 4 or so days (e.g. Day 1, ¼ of the restrictive diet, ¾ of the present diet; Day 2 - ½ of the restrictive diet, ½ of the present diet etc.). The diet trial duration is generally at least 8 weeks. If no significant benefit is noted at the end of this time, a dietary hypersensitivity is usually ruled out. However, it is important to note that patients who begin to benefit from a diet within the 8 weeks may take longer to manifest the maximal benefits of the diet (e.g. 10 to 12 weeks or longer). The diet should be continued until benefit is complete or it has plateaued. Every effort must be made to keep the diet trial strict (no other foods, treats, flavored chew toys, flavored heartworm preventative, flavored joint therapies etc.). Patients are ideally re-checked 1-2 times during the diet trial to assure compliance and examine for the presence secondary infections etc. that may complicate interpretation of the diet. Compliance may be enhanced by having the owners maintain a daily log of “degree of pruritus (e.g. scale of 1-10)” and amount/types of food fed.

It is very important that potentially pruritic pyoderma and/or Malassezia infections be cleared up and controlled, early in the trial diet. It is not uncommon to continue antibiotic therapy or Malassezia topical treatment throughout the diet trial to prevent exacerbation of infection during the trial. It is very acceptable to use an antihistamine, glucocorticoid, oclacitinib or Cytopoint during the
earlier phases of the diet trial to reduce pruritus (i.e. during the first 4-5 weeks). It is very important that these medications be stopped towards the end of the diet trial to see what the diet alone is capable of doing for the problem.

If a response to the diet is noted, the diet should be continued until maximal benefit is achieved. A partial response (e.g. 50%) may suggest the presence of inter-current causes of pruritus (e.g. atopy) unless the diet trial is with a hydrolysate (see above under hydrolysate diets). If a partial response is noted on a hydrolysate diet, it may be worthwhile switching the patient to yet another restrictive diet (e.g. novel protein diet) or home prepared diet to see if complete resolution of the problem is possible, before ascribing residual pruritus to atopy.

The effect of the diet is confirmed by challenge (with the previous diet). Although exacerbations of pruritus may be noted within hours of exposure to a problem food ingredient, the average time to the re-exacerbation of pruritus is 3-7 days; but may take as long as 10-14 days. In the event of an exacerbation of signs, re-institution of the restrictive diet usually produces a more prompt response than was encountered during the trialing period.

Once a diagnosis of a food sensitivity is made, we often encourage our clients to define the proteins are problematic for the patient. Single protein sources can be added to the basal diet at a frequency of one every 10-14 days. This data may allow for the selection of other commercial diets that can be fed in the future (e.g. if the patient tolerates chicken, a chicken based diet can be trialed).

Other therapies:

The signs associated with food sensitivities are variably responsive to glucocorticoids (some may be resistant to anti-inflammatory dosages; some may be very responsive to even low dosages). Antihistamine therapy appears to be less successful when compared to treating atopy in the dog. It remains unclear as to how effective oclacitinib (Apoquel), Cytopoint or Atopica are in treating the pruritus associated with food sensitivity. Our impression is that both oclacitinib (Apoquel) and Atopica may benefit some individuals with food sensitivity. We do not have data on Cytopoint.
Update on the management of canine atopic dermatitis

Rod A.W. Rosychuk, DVM, DACVIM

Colorado State University, Ft. Collins, Colorado, USA

Advances in the management of canine atopic dermatitis have largely come about because of our improved understanding of the pathogenesis of the disease. Atopy would appear to be a genetically predisposed disease wherein affected dogs have an abnormal immunologic response to allergen exposure (T helper lymphocyte 2 as compared to the T helper 1 response seen in normal individuals). Activated TH2 lymphocytes are noted to stimulate the production of B lymphocytes to produce antigen specific IgE. IgE mediates the degranulation of mast cells in the skin to release histamine, serotonin and substance P. Activated TH 2 lymphocytes also produce Interlukin 31 which plays a key role in producing pruritus in the canine. IL 31 works through certain Janus kinase enzyme systems in the cell walls of nociceptive nerves to mediate a pruritic response. IL 31 also works through Janus kinases in lymphocyte walls to, in turn, activate nuclear transcription to produce other pro-inflammatory and pruritogenic cytokines (IL 2,4,6, and 13).

Transcutaneous absorption of allergens appears to be most important in the initiation and perpetuation of atopy. Barrier defects in the stratum corneum of the skin (decreases in the lipid lamellae) appear to be common in atopic dogs. These barrier defects allow for increased transepidermal water loss which promotes drying of the skin and possibly increased transcutaneous absorption of allergens.

Therapies are now available to target many of the above mentioned pathomechanisms.

1. Regular bathing (once every 1-2 weeks during the patient’s allergy season) is often of benefit for reduction of allergen concentration on the skin which may help to reduce transcutaneous allergen absorption, removal or potentially irritating oils/debris from the skin surface and cutaneous rehydration. Cool water baths can give several hours of relief.

2. Topical and oral fatty acid therapy have been noted to improve the lipid barrier defects associated with atopic skin. Topical products such as Dermoscent Essential 6 “Spot On” (unsaturated fatty acids and essential oils) or Douxo Seborrhea Spot on used once weekly may improve coat and skin quality, but, in the author’s experience, their ability to reduce pruritus appears to be relatively small. This point is controversial, because there are claims of reasonable efficacy (e.g. for Dermocent - once weekly application for 8 weeks resulted in a significant (> 50%) decrease in pruritus in approximately 35% of individuals (significantly higher than placebo).

3. Oral fatty acids: Although controversy still exists as to which fatty acids to use in optimizing anti-pruritic effects, products rich in n-3 fatty acids (eicosapentanoic acid, docosahexanoic acid from cold water fish oils and/or flaxseed oil) are favored. They generally benefit patients with milder allergy signs. Lower n-3 fatty acid dosages of 15 to 20 mg/kg per day (these are often “Bottle” dosages), may
produce some degree of improvement in 10-15% of patients. It would appear that higher dosages of omega 3 fatty acid are associated with a higher percentage of individuals who might benefit from supplementation. 30-40 mg/kg/day omega 3 has been associated with improvement in about 30% of patients. Very high dosages (about 70-80 mg/kg/day omega 3) have been associated with producing a greater than 50% improvement in 40-50% of patients. When choosing a routine starting dose of fatty acids, the author usually uses about 30-40 mg/kg/day of a combination of EPA (eicosapentanoic acid), DHA (docosahexanoic acid) and GLA (gamma linolenic acid). Alternatively, 1 tsp or 5 ml/25 kg per day of flaxseed oil has been noted to benefit about 30% of patients. High fatty acid content diets have also been noted to have some anti-pruritic effects. Diets formulated to provide improved “joint” health tend to have the highest omega 3 fatty acid contents. Fatty acid containing products should be given at least a 12 week trial before they are critically evaluated (potentially takes this amount of time to change the fatty acid profile of cellular membranes etc), but some individuals will show improvement within the first 2-3 weeks. The antihistamines used most often and successfully in the management of atopy in the dog are H 1 blockers that have antihistaminic, anti-cholinergic, sedative and local anesthetic effects. They are generally very safe and can be used indefinitely for allergy management. They must be used with caution, if at all, in the presence of liver disease, glaucoma, urinary retention, gastrointestinal atony and pregnancy.

4. Antihistamines: Antihistamines benefit about 20-30 % of atopic dogs. Several are available but one cannot predict which, if any, will be of help in a given individual. The “30%” quoted is the chance of finding an effective antihistamine if you try the entire list! We will generally have the owner try several different antihistamines, each for 2 weeks. The owner notes which antihistamine is being used and what degree of benefit, if any, it may produce. The following are the antihistamines used most frequently in our practice. It is acceptable to use generics. They are listed from most to least effective, although this “impression” of efficacy is highly anecdotal and controversial:

   a. Hydroxyzine HCl (10, 50mg tabs) - 2.2 mg/kg BID
   b. Chlorpheniramine (4, 12mg caps) - .4 - .8 mg/kg (.5 mg) BID to TID
   c. Cetirizine (10 mg tabs) - 10 mg/day/animal < 25 kg and 10 mg BID > 25 kg; or 0.25 mg/kg BID
   d. Diphenhydramine (25, 50 mg caps; most sedative potential of all the antihistamines) - 2.2 mg/kg BID or TID
   e. Fexofenadine (180 mg tabs) - 5.0 - 7.0 mg/kg/day
   f. Amitryptyline - (10, 25, 50, 75, 100 mg tabs) - 2.2 mg/kg BID
   g. Loratidine (10 mg tabs) - 0.5 mg/kg BID
   h. Clemastine (1.34 mg tabs) - .05 mg/kg BID, for dogs under 10 kg 1/2 tab BID; 10 to 25 kg, 1 tab BID, bigger, 1 1/2 tab BID

   Combinations of antihistamines may be of benefit, at times, even when the individual antihistamines themselves appear to have failed. Combinations are most commonly used in individuals with more severe allergic manifestations. Combinations can also be used to “work through the list” of
antihistamines faster during antihistamine trials. The author has had most success using the combination of hydroxyine along with chlorpheniramine, chlorpehniramine and cetirizine or chlorpheniramine and amitriptyline, although any can be used in combination. The antihistamines are used at full dosages and recommended frequencies. The combination of Temaril-P (Trimeprazine and prednisolone; Vanectyl P), used on an every other day basis along with the daily use of another antihistamine (full dosages and frequencies) has also proved to be of significant benefit in reducing dosages of glucocorticoids.

5. Subcutaneous Allergen specific Immunotherapy: selection of antigens for inclusion based on intradermal testing and/or in vitro serologic testing. This treatment modality is noted to benefit 60-70% of patients. Approximately 30%-40% of these will be controlled with just the “shots” themselves; the remaining will require adjunctive therapies (e.g. antihistamines, glucocorticoids etc) to maximize benefit. The average time to onset of benefit is 3-6 months, with the range being 2-12 months. Antihistamines, low dose steroids, cyclosporine or oclacitinib do not appear to affect the onset of benefit from immunotherapy and can be used for pruritus management while awaiting the onset of benefit of immunotherapy. There is some data to suggest that excessive allergen dilution (i.e. too many allergens in a mix) will compromise hyposensitization. Many allergists limit the number of allergens to about 12 in a given mix. However, it has also been suggested that this maximum number may be expanded to as many as 20 allergens, without compromising efficacy. For individuals with larger numbers of allergens deemed necessary to put in the solution, a “2 vial” system is strongly recommended (doubling the volume of hyposensitization solution for each “shot”). Subcutaneous immunotherapy protocols do vary. Our protocol involves giving gradually increasing concentrations and volumes of hyposensitization solutions over the first month (to a total of 1 ml of 20,000 PNU/ml), then once weekly until the maximal benefit of the shots is noted. The frequency of the shots is then gradually reduced. The majority of our patients get “maintenance” shots once every 1-2 weeks, life long. For patients who derive only transient benefits from a given shot (2-3 days), we divide our solutions and give .5 cc twice weekly. Reactions to hyposensitization shots tend to be uncommon. In one recent retrospective study, 27/1,730 dogs started on immunotherapy had reactions. Reactions included 12 that were urticarial, 10 with pruritus and 7 with angioedema. Boxers and English Bulldogs were over represented (Griffin C, NAVDF 2014). Those patients who develop more severe pruritus within 1-2 hours after a given shot, or whose pruritus is escalating after the first few months of the shots (e.g. 6 months) have their volume of hyposensitization solution reduced by 1/2 to .5 cc. Interestingly, others have shown that patients with reactions to immunotherapy may be overall more likely to respond to immunotherapy. For patients not responding after 12 months of hyposensitization, dosages are gradually decreased by 0.2 ml increments every 2 weeks. This may ultimately produce a benefit for those patients whose allergies are actually being perpetuated by reactions to the shots.

6. Sublingual Immunotherapy (SLIT). Allergens are selected based on intradermal testing and/or in vitro serologic testing. SLIT products are now made commercially available by several sources, including HESKA (ALLERCEPT Therapy Drops; given twice daily), IDEXX/Greer (Allerg-g-Complete Drops,
given once daily), Respit (Oralmucosal spray), Nelco (Allerpaws), BioMedical Servies (ACTT Allergy Drops). Many Dermatologists formulate their own products. Allergens are in a glycerinated base (not the same aqueous solution used in conventional, subQ immunotherapy protocols). In a Heska study of 217 treated dogs, after 6 months, 68/124 (55%) showed a good to excellent response. In 47 dogs who failed injection immunotherapy (failure; adverse reactions; compliance difficulties), 23/47 (49%) were noted to respond. Our success rates with this treatment modality mirror those reported. Take home message: overall success rates, time to onset of benefit associated with SLIT- similar to those associated with subcutaneous immunotherapy; may work when subcutaneous “shots” have failed. The trial period recommended for SLIT is 12 months. It is suggested that SLIT may be used safely in patients with histories of reactions to immunotherapy. In such cases, it is started at a weaker dilution. Reactions are uncommon and include rubbing/scratching at the mouth, vomiting or worsening of allergy signs. If noted, the dosage is decreased.

7. Intralymphatic Immunotherapy: Rational for use: few injections of very small volume of allergens will produce prolonged duration of clinical anti-pruritic benefit. In one recent study of 20 atopic dogs treated with alum precipitated allergens, ultrasound guided injections in to the popliteal lymph nodes werer given every 4 weeks for 3-7 times and patients were evaluated over 28 weeks. There was a good response to therapy in 60% (Fischer at al, 8th WCVD, 2016). In another study, 51 atopic dogs were given 4-6 ultrasound guided injections (0.1 ml, 200 PNU) in the popliteals once monthly and were re-evaluated at 1,2,3,6 and 12 months. 21 dogs completed the study. After 2-3 months, significant improvement was noted that lasted 12 months (Timm K et al, 8th WCVD, 2016).

8. “Non specific” or “Shotgun” hyposensitization is available in the USA through RESPIT ™. Allergens for inclusion (20) are chosen based on what are thought to be the major allergens in the patient’s geographic area. In a recent report (abstract presented at the 8th WCVD), in 103 patients that were followed for at least 270 days or more, there was an excellent response in 19.4%, good in 37.9%, fair in 25.2% and poor in 17.5%. In this retrospective, non controlled study, the combined good-excellent effectiveness rate of RESPIT injectable (57%) was similar to rates previously reported for ASIT in atopic dogs. RESPIT may be an option for those atopic patients that consistently test negative (by either intradermal testing or in vitro serologic testing; estimated to be about 10% of the atopic population).

9. “Rush” Immunotherapy involves giving all the induction dosages in the hyposensitizing protocol in one day (shots given SubQ, once every ½ hour; monitoring closely for any signs of reactions). If a reaction is noted, the protocol is stopped. The highest volume/concentration attained in the “Rush” is then sent home as the weekly maintenance dose. Rush immunotherapy has been shown to produce a slightly (5-10%) more rapid onset of benefit and higher percent success rate, compared to conventional immunotherapy. Following the “Rush” induction, the patient remains on the weekly maintenance dose (usually 1 ml) until the maximal benefit of the shots has been noted. Rush immunotherapy is primarily recommended for those patients who are more severely affected (desiring a more rapid onset of benefit) or for owners who are not able or willing to give the more frequent shots (once every other day) during the induction period.
10. Cyclosporine (microemusified; Atopica, Elanco/Novartis; marketed in 10 mg, 25 mg, 50 mg and 100 mg capsules). Generics are available and may be less expensive. While generics are noted to have equal bioavailability with Atopica, their clinical efficacy is variable compared to Atopica. Prior to using a generic, it is likely of most benefit to prove the efficacy of cyclosporine therapy with Atopica, then, once the problem has been stabilized, switch to the generic to see if it provides the same degree of control. The therapeutic dose most commonly used for treating atopy is 5 mg/kg/day. We often gradually work up to this dose over several days to minimize deleterious GI side effects. Cyclosporine has been noted to produce good to excellent results in 70-80% (75%) of cases. The overall beneficial effects have been shown to be similar to those of prednisolone or methylprednisolone, without the attendant deleterious side effects of the steroid. Onset of benefit usually within 2-4 weeks. It may take 2-3 months to see the maximal benefits of the drug. Trial therapy should be 45-60 days. Once the maximal beneficial effect has been noted, the frequency of administration is reduced to every other day (40 % may be controlled at this frequency), then every 3rd day (about 15-20% may be controlled at this frequency). For patients who are not able to be controlled with a decrease in frequency, the daily dosage can be reduced. We actually work within a dosage range for Atopica (5-10 mg/kg/day). If a partial response is noted at 5 mg/kg/day, we will increase the dose (e.g. to 7.5 mg/kg/day) and this will often improve upon pruritus control. Cyclosporine should ideally be given on an empty stomach (i.e. at least 2 hours before or after feeding) to enhance absorption. However, in order to reduce the incidence of gastrointestinal side effects at the initiation of cyclosporine therapy, it is often given with a small amount of food. After 1-2 weeks, assuming the drug is well tolerated, it can then be given without food, to enhance absorption. Some individuals simply will not tolerate the drug well unless it is given with food. If such is the case, food is given with cyclosporine (long term). In many individuals, this will not affect the clinical response to the cyclosporine. Side effects - most commonly gastrointestinal upsets, especially vomition. May also see diarrhea, flatulence, abdominal discomfort, inappetance. If gastrointestinal signs are noted, the cyclosporine should be stopped until the signs abate. The drug can then be started again, given with a small amount of food. Many individuals appear to develop a tolerance to the drug after this withdrawal and re-introduction protocol. Freezing the capsule will very significantly reduce the tendency towards vomition. We know that freezing the capsules for as long as one month prior to administration does not affect the cyclosporine nor its bioavailability. Pre-treatment with maropitant or metoclopramide may also resolve this tendency to vomit the drug. Other side effects include gingival overgrowth which occurs in 5% of dogs on just cyclosporine alone; 12% with the ketoconazole/cyclosporine combination. Overgrowth appears to be related to dose (higher incidence with higher the dose). Once noted, some of the signs may be reduced by providing dental hygiene (e.g. brushing, rinses) although this is usually not effective. Variable responses (usually only partial - e.g. at best 30% improvement) may be seen to oral azithromycin (10 mg/kg SID for 6 weeks; intended to work while patient is left on cyclosporine) or azithromycin formulated in a toothpaste (8.5%; available from compounding
pharmacies; daily brushing). Complete resolution of gingival overgrowth requires discontinuation of the cyclosporine. Variable degrees of reduction in gingival overgrowth may be seen by reducing the daily dose or going to less frequent administration. If the drug is stopped and gingival overgrowth resolves, some individuals will be able to return to cyclosporine therapy and not re-develop the overgrowth. Most will have recurrence. If cyclosporine must be maintained, overgrowth can be transiently dealt with by gingival resection (e.g. surgery or laser). Overgrowth will usually gradually recur. Papillomatosis may develop at any time on cyclosporine (can see as early as 2-3 weeks in to treatment). Discontinuation of the cyclosporine usually results in prompt resolution of the problem. UTI’s are noted to develop in about 15% of patients on chronic cyclosporine therapy; 25% if on concurrent glucocorticoids - warranting the periodic performance of urinalyses and urine cultures in patients who are on long term, maintenance regimens (i.e. usually recommended once yearly). Other side effects that may be seen include hirsutism, and rarely, bacterial pyoderma, nephropathies, bone marrow suppression and a lymphoplasmacytic dermatosis. In that cyclosporine is expensive, it has been used in conjunction with ketoconazole to increase the blood concentrations of cyclosporine. The mechanism for this decrease in clearance is probably a combination of the inhibition of cytochrome P-450 in the liver (reducing the clearance of the drug) and p-glycoprotein in the intestine (that would ordinarily pump absorbed oral cyclosporine back into the intestine). When the drugs are used in conjunction, we tend to start with 2.5 mg/kg cyclosporine per day along with 2.5 mg/kg/day ketoconazole once per day. The actual dosage range for ketoconazole is 2.5-10 mg/kg/day. In some dogs, higher circulating dosages of cyclosporine may be achieved with a higher dose of ketoconazole. The ketoconazole and cyclosporine are usually given with a small amount of food initially to reduce the incidence of GI upsets. If the combination is well tolerated after 1-2 weeks of therapy, then the ketoconazole is given with a small amount of food (to enhance its absorption), and the cyclosporine is given about 2 hours later (on an empty stomach, to enhance absorption). In the past there was a significant cost benefit associated with giving the ketoconazole/cyclosporine combination. More recently, ketoconazole has become much more expensive and a significant cost benefit may only be realized with large dogs. Approximately 10-15% of individuals who have been on oral cyclosporine for many months to a couple of years and have been in complete remission, may have their cyclosporine discontinued...and not have the disease relapse. A cure! Cyclosporine often does not do as good a job of controlling allergy related otitis externa as it does for controlling the more generalized pruritus associated with allergy (i.e. otitis may remain a problem in the face of good generalized control of allergic signs).

11. **Oclacitinib (Apoquel, Zoetis).** Oclacitinib is a Janus kinase (JAK) inhibitor which selectively inhibits JAK-1 dependent enzymes responsible for the production of pro-inflammatory cytokines (IL-2,4,6,13) and interleukin 31 which induces neuronal itch stimulation. At the recommended dose, oclacitinib has minimal effects on JAK-2 (involved in hematopoiesis and innate immune responses) and JAK-3 dependent enzyme systems. A recent study (abstract presented at the 8 WCVD, 2016) has suggested that Apoquel therapy may actually retard the onset of sensitization to other allergens (was shown with Bermuda grass antigen ). In this sense, it is possible that it is protective with respect to developing
“new” sensitivities to various allergens. The recommended protocol for its routine use is to give a dose of 0.4-0.6 mg/kg BID for two weeks, then this dose once daily thereafter. In the original efficacy studies (299 dogs), 60-66% of dogs were considered treatment successes by the owner; 49-56% were considered treatment successes by Veterinarians. We quote an 80% initial response rate (initial BID therapy). But we also note that about 20% of these individuals will not be as well controlled on once daily therapy (see below). Apoquel is also noted to produce variable anti-pruritic effects in dogs with adverse food reactions, scabies and flea allergy dermatitis. It is labelled for use in dogs ≥ 1 year of age. The drug is overall very well tolerated. Potential side effects include gastrointestinal upsets (usually mild and transient), weight gaining, behavioral changes, leukopenia (appears to be rare); elevated liver enzymes (rare; specifically alk. phos. - significance unknown), demodicosis (rare; product of immunosuppression?). Although laboratory monitoring is often recommended during therapy, the incidence of finding abnormalities is very low. When monitoring (CBC, serum chemistry panel, urinalysis) is done, it is done at time 0 (baseline), 3 months, 6 months after this, then yearly thereafter. Although a higher incidence than normal of urinary tract infections has been noted in individuals on other immunosuppressives such as glucocorticoids and/or cyclosporine, to date, no significant increase in infections has been noted in dogs who have been on oclacitinib. In a recent CSU prospective study done on 60 dogs who had been on oclacitinib for 6 months, no dogs were noted to develop urinary tract infections. We do not do urine cultures as part of the screening battery of tests when monitoring for side effects of the drug. Response to therapy is often very prompt...within hours to 1-2 days. Similarly, escape from control is also noted very quickly after stopping the drug (often within 1-2 days). With the shift to once daily therapy, it is not uncommon to see a worsening of pruritus. If this is encountered, improved pruritus control is often noted to slowly improve over 2-4 weeks in many of these individuals. However, less than ideal control of pruritus may be noted to persist in 20-30% of patients. Options to consider when this occurs include: if the anti-pruritic effect tends to wane during the latter part of the day, you can change the time of administration (giving it in the evening instead of the morning). Increasing the dose to the highest end of the recommended dosage range - i.e. 0.6 mg/kg/day. Only a subtle increase in dose is sometimes noted to benefit patients very significantly. Add an antihistamine or even two antihistamines to the treatment regimen. Even if these antihistamines had been tried in the past and failed to be of benefit, they may have some affect when used with oclacitinib. Consider dividing the daily recommended dose (0.6 mg) in to two smaller, equal dosages. More frequent dosing over a 24 hour period may potentially be associated with a higher incidence of immunosuppression (e.g. demodicosis) or bone marrow suppression (e.g. leukopenia), but these appear to be rare. It is important to note that it is reasonably common to have the otitis associated with atopy (environmental allergy) not respond as well to oclacitinib as do the cutaneous manifestations of the disease (i.e. the patient’s pruritus is well controlled, but “flares” of otitis are still encountered or the ears remain a continued source of problem). Such individuals may have to be maintained on chronic topical steroid therapy to optimize otitis control. Apoquel can work when Cytopoint has failed.
12. **Cytopoint (Canine Atopic Dermatitis Immunotherapeutic, lokivetmab; Zoetis)**

Cytopoint is a caninized (developed in the dog; would not be suitable for use in the cat), monoclonal antibody that is directed at interleukin 31. The antibody complexes with IL 31 and the complex is then biodegraded. Because of its specificity of attack and benign “clearing” from the body, it is a very “safe” therapy in the dog. The antibody is given by subcutaneous injection. A dramatic reduction in pruritus is noted quickly.

In a recent retrospective study performed at CSU by Dr. Clarissa Souza, 135 dogs were treated with Cytopoint. In these 135 treated dogs, 56% showed very significant reduction in pruritus within 24 hours, 40% between 1 and 3 days and 5% in 3 or more days. 116/132 (87.8%) of cases achieved satisfactory client assessed pruritus control. The average time for which a given “shot” controlled pruritus was 4 weeks, but it did vary from 2 weeks to 6-7 weeks. In this same retrospective study, the required frequency of administration was 2-3 weeks (1 dog), 3 wks (6 dogs), 3-4 wks (4), 4 wks (26 dogs), 4-5 wks (6), 5 wks (4), 6 wks (4), 7 wks (3 dogs). A tendency for the “shots” to not work as long as they did originally has been noted with season change in some dogs (i.e. during the winter, a given “shot” working for 4-5 weeks; with the coming of spring may only work for 3-4 weeks etc.)

On a rare occasion, after receiving one injection that was beneficial, subsequent “shots” failed to be of benefit. Advantages:

- **a.** Very safe; can be used in any aged individual (no age restriction as seen for Apoquel).
  - Can be used with any other medications (e.g. can be used for older dogs who are on polypharmacies).
- **b.** The drug can be used for “flares” of allergic dermatitis (e.g. “once”), for seasonal control of allergies and for long term, non seasonal management.
- **c.** Cytopoint can work when Apoquel has failed. In the Cytopoint study above (135 dogs treated with Cytopoint), 71 had been previously treated with Apoquel and in 65 of these, the Apoquel failed to control pruritus. 55 of these dogs responded to Cytopoint. Cytopoint has worked to control pruritus in some dogs where virtually all other therapies have failed (including Apoquel, Atopica, immunotherapy).

Disadvantages:

- **a.** Cost (especially in large breed dogs); expensive.
- **b.** Side effects: in the retrospective study of 135 treated dogs, side effects included lethargy (8), vomiting (2), hyperexcitability (1), pain at the injection site (1) and urinary incontinence (1). All side effects were transient and did not require discontinuation or alteration of the treatment regimen.
- **c.** Allergy related otitis externa may not be as well controlled as the cutaneous manifestations of allergy. Such patients often respond well to long term, maintenance topical steroid therapy (see Long term management of allergic otitis externa in these proceedings).
Autoimmune/immune mediated skin diseases

Rod A.W. Rosychuk, DVM, DACVIM

*Colorado State University, Ft. Collins, Colorado, USA*

Canine Autoimmune/Immune Mediated Diseases (Partial List)

- Pemphigus foliaceus
- Pemphigus vulgaris
- Discoid Lupus erythematosus
- Generalized Discoid Lupus Erythematosus
- Systemic Lupus Erythematosus
- Symmetric lupoid onychodystrophy
- Vesicular cutaneous lupus erythematosus
- Subepidermal blistering diseases
  - e.g. Mucous membrane pemphigoid;
  - Bullous pemphigoid
- Vasculitis/Vasculopathy
- Proliferative arteritis
- Dermatomyositis
- Cutaneous uveodepigmentation syndrome
- (Vogt-Koyanagi-Harada-like syndrome)
- Erythema multiforme
- Toxic epidermal necrolysis
- Sterile Granuloma/pyogranuloma Syndrome
- Sterile Panniculitis
- Cutaneous reactive histiocytosis
- Systemic histiocytosis
- Perianal fistula

Overview:

The most common autoimmune diseases seen in the dog are pemphigus foliaceus and discoid lupus erythematosus. However, even these diseases are uncommonly seen in clinical practice. The others listed above are only rarely encountered.

In general, autoimmune diseases are usually inflammatory, with various degrees of crusting, +/- vesicobullous lesions, +/- various degrees of erosion or ulceration. They often result in depigmentation of the skin (pigment falling from the epidermis into the dermis - a process called pigmentary incontinence wherein pigment is then taken away from the area by melanophages; depigmentation also comes from damage to melanocytes). They may affect mucous membranes (SLE, Pemphigus vulgaris, Bullous pemphigoid, EM, TEN, drug eruption).

Skin lesions often have a symmetrical distribution. Because the epidermis of the canine is thin (compared to man), pustular and vesicobullous lesions (e.g. as seen with pemphigus) tend to break rapidly following formation. We often see only remnant inflammation, crusting and erosion. Some autoimmune skin disease may be associated with systemic symptomatologies like fever, depression, anorexia, leukocytosis (e.g. Pemphigus foliaceus or vulgaris) or multiple organ-system disease (e.g. systemic lupus erythematosus). In the dog, the major differential diagnoses for most autoimmune diseases include bacterial pyoderma; demodicosis; dermatophytosis; zinc responsive dermatosis; drug eruption; superficial necrolytic dermatitis and cutaneous neoplasia. In the cat, the major differential diagnoses would be dermatophytosis, demodicosis, bacterial pyoderma, drug eruption and neoplasia.
In general, the diagnosis of autoimmune diseases is based on history, physical examination, cytology (e.g. looking for acantholytic keratinocytes to support a suspicion of pemphigus) and skin biopsy. Skin biopsy is the most valuable diagnostic aid. General guidelines for sampling:

a. If possible, biopsy entire primary lesion - vesicles, bullae, pustules. Ideally, take entire structure with a small amount of perilesional tissue for histopathological examination.
b. Junctional biopsy - margin of lesion is where you will often see more classic histologic changes
c. Lesional biopsy
d. Biopsy through crusts (if present).
e. Should biopsy all morphologically distinct lesions

Detection of autoantibody in the skin by direct immunoflorescence testing (requires special transport media - Michel’s media) or immunoperoxidase staining (can use formalized sample) - helps better document the problem as autoimmune and helps differentiate the type of autoimmune disease by documenting the presence and delineating the pattern of autoantibody deposition respectively. However, these tests are prone to false negatives and false positives. Because we are able to do quite a good job with respect to histopathologic evaluation without these tests, they are almost never done in clinical or Specialty Dermatology practice.

At some point during the work-up (definitely prior to instituting any potent immunosuppressive therapy), a general laboratory screening including CBC, serum biochemistries and urinalysis should be performed. This will help in the delineation of concurrent unrelated organ disease or related organ disease such as the proteinuria suggestive of a glomerulonephritis seen with SLE. The screening also allows for the establishment of baseline values prior to initiating potent immunosuppressive therapy.

Assessing response to immunosuppressive therapy also contributes to the confirmation of an autoimmune disease. Most autoimmune problems will respond to parenteral glucocorticoid therapy. Overview of the treatment options for the management of canine and feline autoimmune/immune mediated diseases:

**Pemphigus foliaceus:**
- Prednisolone/prednisone monotherapy
- Dexamethasone monotherapy
- Mycophenolate mofetil +/- glucocorticoid
- Azathioprine and glucocorticoid
- Tetracycline or doxycycline and niacinamide (30-40% of chronic facial; 10-15% generalized)
- Cyclosporine - 4 - 5 mg/kg BID to initiate +/- glucocorticoid
- Cyclosporine and azathioprine +/- glucocorticoid
- Cyclosporine and mycophenolate +/- glucocorticoid
- Human immunoglobulin (to initiate)
- Topical tacrolimus (for focal lesions)
Discoid Lupus Erythematosus
- Topical tacrolimus - response rate - 60%
- Tetracycline or doxycycline and niacinamide - response rate - 60%
- Combination of tacrolimus and doxy./niacinamide
- Oral prednisone/prednisolone (monotherapy)
- Hydroxychloroquine - overall response rate unknown
- Azathioprine and glucocorticoid
- Cyclosporine - 5 mg/kg/day to initiate therapy

Vesicular Cutaneous Lupus erythematosus
- Prednisone/Prednisolone monotherapy
- Azathioprine/glucocorticoid - most commonly used
- Tetracycline or doxycycline and niacinamide

Symmetric Lupoid Onychodystrophy
- Omega 3/6 fatty acids
- Pentoxifylline - 50 - 60% responders
- Tetracycline or doxycycline and niacinamide - 50 - 60% responders
- Cyclosporine - starting at 5 mg/kg/day
- Prednisolone/Prednisone monotherapy

Idiopathic Erythema Multiforme
- Prednisone/prednisolone monotherapy
- Cyclosporine - starting at 5 mg/kg/day
- Azathioprine and glucocorticoid
- when due to drug eruption: Glucocorticoid; consider initiating therapy with IV immunoglobulin

Idiopathic Immune Mediated Vasculitis
- tacrolimus (topical)
- Pentoxifylline
- Pentoxifylline and glucocorticoid (combination is preferential)
- Glucocorticoid and azathioprine
- Cyclosporine - starting at 5 mg/kg/day
- Sulfasalazine
- Dapsone

Proliferative Arteritis (e.g. St. Bernard)
- Tacrolimus (topical)
- Oral glucocorticoid
- Oral glucocorticoid and tetracycline or doxycycline and niacinamide
- combination of all the above
Sterile Granulomatous/Pyogranulomatous dermatitis and/or panniculitis
- cyclosporine - starting at 5 mg/kg/day
- prednisolone/prednisone monotherapy
- tetracycline or doxycycline and niacinamide
- tacrolimus

Dermatomyositis
- Pentoxifylline
- Pentoxifylline and prednisone/prednisolone
- Glucocorticoid monotherapy
- Tetracycline or doxycycline and niacinamide
- Cyclosporine - starting at 5 mg/kg/day

Perianal Fistual
- Tacrolimus - 50% responders
- cyclosporine - starting at 4-5 mg/kg BID - 80% responders
- Glucocorticoid
- Glucocorticoid and azathioprine

DRUG SPECIFICS

Glucocorticoids
Canine: 1.5-4 mg/kg/day prednisone or prednisolone to initiate therapy. Author’s most commonly used protocol: 2 mg/kg/day for 2 weeks (this divided and given twice daily), then 1 mg/kg/day for two weeks (this again divided and given twice daily), then 0.5 mg/kg/day given once daily for 2 weeks, then 1.0 mg/kg given once every other day for two weeks, then 0.5 mg/kg every other day. Goal for long term maintenance - < 0.5 or 0.25 mg/kg eod. If, after 1-2 weeks at 2 mg/kg/day a significant response is not seen, this dose can be increased to 3-4 mg/kg/day. Another option for cases that do not respond to 2-3 mg/kg/day over the first 2-4 weeks of therapy would be to switch to oral dexamethasone at 0.2 mg/kg/day. This is given daily for two weeks, then reduced to 0.1 mg/kg for 2-4 weeks. Once remission has been achieved, the patient is switched back to prednisone/prednisolone therapy, starting at 1-2 mg/kg/day for longer term treatment (this dose is then gradually tapered, as noted above). There is a great deal of individual variation regarding susceptibility to glucocorticoid side effects. Side effects are very common at these more aggressive starting dosages, including polyuria, polydipsia, polyphagia and weight gain (if food intake is not controlled); less commonly panting, behavior changes, muscle weakness, muscle atrophy. With longer term therapy (months and longer), if dosages are excessive, other side effects that may be encountered include hair loss, cutaneous atrophy, muscle atrophy, muscle weakness, ligament rupture, predisposition to cutaneous infections and urinary tract infections and calcinosis cutis. As many as 40%-50% of dogs receiving chronic glucocorticoids develop
urinary tract infections. In many instances, they are not symptomatic for these infections (will only be documented by urinalysis/urine culture). Patients who are on chronic glucocorticoid therapy should be monitored on a regular basis (for example, CBC, serum chemistry panel, urinalysis, urine culture every 6-12 months). The finding of a worsening steroid hepatopathy (increased Alkaline Phosphatase, much milder increase in ALT) is, in itself not a threat to liver function, but is an indicator of the fact that the individual may be “seeing” too much glucocorticoid. Minimizing glucocorticoid side effects is largely achieved by trying to reduce dosages as quickly as possible to lowest every other day maintenance regimens. Owners should be proactive with respect to managing food intake (limiting food intake; feeding lower calorie diets; “bulking out” the diet by adding low calorie vegetables such as green beans; treating with lower calorie foods such as green beans or carrots). If glucocorticoid side effects are significant or dosages cannot be reduced to those expected to be well tolerated for long term therapy, then consideration should be given to using steroid sparing drugs, along with the glucocorticoid (e.g. mycophenolate, azathioprine, chlorambucil) or alternative therapies such as cyclosporine.

Feline: Prednisolone: 2-6 mg/kg/day to start (we generally start in the 3 mg/kg/day range). The goal for long term, maintenance therapy is < 1-1.5 mg/kg q 48 h. Cats who do not respond well to more aggressive dosages of prednisolone - try triamcinolone acetonide - 0.4 - 0.8 mg/kg/day; decrease to < 0.1 mg/kg eod OR oral dexamethasone can be used at a dosage of 0.2 to 0.4 mg/kg/day.

Tetracycline or doxycycline and Niacinamide (canine)

500 mg of both tetracycline and niacinamide per dog (250 mg/kg if < 10 kg) given TID for a 2-3 month trial. Tetracycline may be replaced with doxycycline, 5-10 mg BID (we generally start with 5 mg/kg BID). 3-4 weeks to onset of benefit. Once remission achieved, reduce doxy to once daily; niacinamide to twice daily for a couple of months then maintain on once daily doxy and once daily niacinamide long term (usually cannot get to every other day therapy for long term management with these drugs).

Tacrolimus (Protopic, Fugisawa) (canine)

Similar mode of action to cyclosporine. Topical; 0.1% BID to start. Very, very expensive, but a little goes a long way!

Pentoxifylline (canine)

Used to improve vascular perfusion and has anti-inflammatory effects. 10-25 mg/kg given BID or TID. We usually initiate most therapies with 15-20 mg/kg BID. Well tolerated.

Azathioprine (canine only)

Azathioprine is generally used concurrently with glucocorticoids (dosages, as outlined above), with an overall goal of being able to eventually reduce the amount of glucocorticoid required to control
the problem. It is uncommon to be able to control dermatologic problems with just azathioprine alone. Azathioprine therapy is initiated at 2 mg/kg/day (or 50mg/m²) for 4-8 weeks until significant clinical improvement is noted. The dosage is then reduced to this dose given once every other day. It has been suggested that the onset of benefit for diseases associated with cytotoxic lymphocytes (e.g. lupus diseases) may be faster (2-3 weeks) than for diseases mediated by autoantibodies (6-8 weeks; takes longer time for antibody concentrations to go down). Some have suggested it may take as long as 12-16 weeks to see the maximal effect of this drug. Major toxicities: Hepatotoxicity - usually seen within the first 1-4 weeks of therapy. In many instances this will only be manifest as increases in liver enzymes. In others, individuals will become inappetant, anorexic, depressed and develop GI signs (i.e. vomition). Liver enzymes are examined pre and 2 and 4 weeks after initiation of therapy. If liver enzymology changes are seen, but the patient appears healthy, azathioprine is stopped until the enzymes are normalizing, then started again at a lower dosage (e.g. 50 mg/m² given once every other day). If the patient becomes ill (anorexia, vomition, depression) in association with liver enzymology changes, the drug must be stopped and alternative therapies should be considered. If therapy is maintained in the face of liver changes, overt liver failure and death may occur. The overall incidence of hepatotoxicity had been low, but, within the last few years, the incidence has increased. It is not clear as to why this phenomena has occurred. It has been suggested that this maybe related to the use of generic products (the brand name product is Imuran®). Myelosuppression - This is most commonly associated with daily therapy. It is uncommon. It is suggested that CBC’s and platelet counts be done every 2-3 weeks while on daily therapy, then 2 weeks after going to every other day therapy, then 3-4 weeks after this, then in 3 months, then 6 months, then every 6-12 months thereafter. If myelosuppression is noted, the drug is stopped until counts normalize, then can be re-started at a lower dosage (e.g. if started on 2 mg/kg/day, reduce to 50 mg/m² given once every other day). Other rare toxicities reported include vomition, diarrhea, pancreatitis, predisposition to infection and neoplasia. Azathioprine is not used in cats because of the proven high incidence of myelosuppression with the drug. Assuming the patient is doing well, the dose of azathioprine can be decreased by 25% for every 6 months of excellent disease control. However, the dosage is usually not reduced to less than 1 mg/kg every other day for long term maintenance.

Azathioprine has been used to treat most immune mediated diseases. It may produce a faster time to onset and may be overall more effective for lymphocyte mediated diseases (especially the lupus group of diseases, uveodepigmentation syndrome).

Chlorambucil (canine and feline)

Because of its high cost, chlorambucil has been used most commonly in cats and small dogs. Chlorambucil is often considered as an alternative to azathioprine because it is overall better tolerated. In the dog, it is less likely to cause hepatopathies than azathioprine. It is a steroid-sparing agent of choice in the cat. Side effects are uncommon and include myelosuppression, anorexia,
vomition, diarrhea, urticarial reactions and hepatotoxicity. The dosage is 0.1-0.2 mg/kg/day along with prednisone/prednisolone, triamcinolone (cats) or dexamethasone (cats) at the glucocorticoid dosages outlined previously. Once approximately 75% remission has been achieved (usually 2-4 weeks), the dosage is reduced to every 48 hours. Monitoring for side effects (CBC, platelet count and liver enzymes) is done every 2-3 weeks while on daily induction dosages. The frequency of monitoring is then dramatically reduced (e.g. 1-2 months after being on eod therapy; then in 3-4 months, then every 6 months thereafter).

**Mycophenolate mofetil (canine)**

Similar mode of activity to azathioprine, but not associated with myelosuppression, hepatotoxicity and pancreatitis. 2-4 weeks to onset of benefit. Potential side effects are diarrhea (can be very severe), gastrointestinal hemorrhage, vomition and/or anorexia. 10-20 mg/kg BID (we start at 10 mg/kg BID) to initiate therapy. Higher dosages are associated with a higher incidence of gastrointestinal upsets. Once good control has been established, the dose is decreased to once daily for a couple of months, then once every other day. If initiated therapy with glucocorticoids and mycophenolate, slowly taper and then discontinue glucocorticoids and try to maintain on mycophenolate alone. Consider monitoring blood work at 2 weeks, a month, then 3-4 months after this, then every 6 months thereafter.

**Leflunamide (canine)**

Well tolerated drug, but, on occasion can cause myelosuppression (thrombocytopenia, leukopenia), gastrointestinal upset and liver toxicity. 2-4 mg/kg/day (lesser dosages associated with lesser incidence of gastrointestinal upset). To date has been used to treat cutaneous reactive histiocytosis.

**Cyclsoporine**

Canine: induction dose somewhat dependent on disease being treated (see above for specific diseases). In 5-10 mg/kg range. More predictable immunosuppression with BID therapy to initiate (e.g. 5 mg/kg BID). Treat with the starting dose until in remission and then gradually reduce dose. For pemphigus foliacues - 5 mg/kg BID until remission and a month beyond remission, then 5 mg/kg/day for a couple of months, then 5 mg/kg every other day for a couple of months, then 5 mg/kg every third day. For diseases wherein the starting dose is 5 mg/kg/day, use this until remission achieved and one month beyond, then 5 mg/kg every other day for a couple of months, then 5 mg/kg every third day. Recommend Atopica (Elanco). Generics somewhat erratic with respect to efficacy. The dosage of cyclosporine can be reduced by ½ by concurrently giving it with ketoconazole (5 mg/kg/day; 2 hours before giving cyclosporine). Goal is to gradually reduce frequency (i.e. eod, then twice weekly) and then dose for long term maintenance. If unable to reduce frequency, slowly reduce daily dose. Side effects: vomition, diarrhea, nausea, abdominal pain, flatulence, borborygmus, gingival overgrowth, papillomatous, hirsutism and rarely trembling, seizures, hepatopathy, lamneness, opportunistic infections (bacterial, fungal), toxoplasmosis (feline).
Feline:

Cats are generally started on the “label” dose for Atopica (7 mg/kg/day; the dose used for the management of allergic skin disease). The dose range for cyclosporine is 5-10 mg/kg/day. Side effects (in decreasing order of frequency) include vomition, retching, diarrhea, weight loss, decreased appetite, lethargy, hypersalivation, behavior change and gingivitis. We gradually work up to the target dose over several days to reduce the incidence of gastrointestinal side effects (vomition) and also initially give the cyclosporine with food. As for the canine, if there is concern because of lack of response or potential immunosuppression/toxicity, consideration can be given to measuring trough or peak cyclosporine concentrations. Values above 1,000 ng/ml (trough) are noted to be immunosuppressive (patients at greater risk of developing opportunistic infections). Cyclosporine has been very effective in treating pemphigus foliaceus and plasma cell pododermatitis in cats.

Hydroxychloroquine (canine)

Hydroxychloroquine is an anti-malarial drug with anti-inflammatory effects. It is given at a dose of 5-6.5 mg/kg/day. It has been used only rarely in dogs, but does appear to be well tolerated. In humans it has been associated with GI upsets (more acutely), but most importantly with retinopathies in patients on chronic therapy (years). Although retinal disease has not been noted in the dog in the few dogs followed, they were also only followed for several months (not years). The only report of hydroxychloroquine use to date is in the treatment of cutaneous lupus.

Human Intravenous Immunoglobulin (canine)

This product is essentially made up of non modified IgG immunoglobulin (95%). IgG is noted to saturate Fc receptors on macrophages and to also bind to T and B lymphocytes to moderate their function. Dose: 1 mg/kg (dose range of 0.5-1.5 mg/kg) given IV over 6-12 hours. This product is very expensive. HII has been used to initiate therapy for drug eruption, pemphigus, erythema multiforme and toxic epidermal necrolysis.

Pemphigus Foliaceus

Pemphigus foliaceus is the most common autoimmune skin disease seen in the dog and cat. Autoantibody binds to the desmosomes of the epidermis (which hold epidermal cells together). This initiates a cascade effect that results in the degradation of adhesion cell surface molecules which, in turn results in the separation of keratinocytes (a process called acantholysis). The spaces that are created as keratinocytes separate are rapidly filled with neutrophils and variable numbers of eosinophils. Clinically, the lesions created look like “pustules” (especially with pemphigus foliaceus) or vesicles or bullae (with pemphigus vulgaris) on the surface of the skin. Cytologically, acantholytic keratinocytes are seen as dark staining, large (size of 3-4 neutrophils), rounded cells. They may be singular or in groups. Normal keratinocytes tend to have more angular margins. Where the split in the skin occurs dictates which of the pemphigus diseases one is dealing with (subcorneal splitting with
pemphigus foliaceus, suprabasilar splitting with pemphigus vulgaris). Because the pustular lesions tend to break very readily, the lesions are usually seen as focal areas of inflammation and crusting with various degrees of erosion.

While the vast majority of cases of PF are idiopathic autoimmune diseases, it is also possible to see the disease initiated by drugs (i.e. drug eruption - trimethoprim-sulfa; meteflumizone-amitraz as Promeris; fipronil-amitraz- methoprene as Certifect).

The breed incidence for canine pemphigus foliaceus appears to vary somewhat with the study. In one, the Bearded Collie, Akita, Chow Chow, Newfoundland, Schipperke and Doberman Pinscher were overrepresented. In a more recent report, the Akita, English Cocker Spaniel, Chow Chow, Shar Pei and Collie were at greater risk. We have seen lines of Chow Chows and Akitas affected. The disease appears to more commonly affect younger to middle aged dogs (2-6 years of age) although all ages of dogs appear susceptible.

Lesions are superficial pustules, focal areas of inflammation and crusting and occasionally epidermal collarettes. Pruritus is variable, but can be intense. In the dog, lesions are most commonly noted over the bridge of the nose, nasal planum, medial aspect of the pinna, periocular region, foot pads and and junctions of the foot pads and interdigital skin. Lesions are usually symmetric. Lesion progression is relatively gradual (in one study 1-3 months in 25% of dogs, 3-12 months in 50% and 1-3 years in 25%). Systemic signs are variable (e.g. depression, fever). Variants of the disease include a form restricted to the feet (footpads, pad/skin junctions) and a chronic facial form (lesions restricted to the face).

Biopsies show broad, subcorneal pustules containing well preserved neutrophils, variable number of eosinophils and variable numbers of acantholytic keratinocytes. Overlying crusts should be examined for acantholytic keratinocytes. Dermal inflammation is superficial and perivascular to interstitial and consists of neutrophils, eosinophils, macrophages, lymphocytes and plasma cells. Pigmentary incontinence may be seen as can a lichenoid pattern of dermal inflammation.

In our clinic, mild cases of canine PF are treated with glucocorticoids alone. Mild to moderate, chronic facial cases are treated with steroid monotherapy; about 40% may respond to doxycycline/niacinamide. Only about 10% of our generalized PF cases respond to doxycycline/niacinamide. Moderate to severe cases are started on glucocorticoids and mycophenolate. Mycophenolate failures are treated with cyclosporine or azathioprine (chlorambucil for smaller dogs).

**Feline**

Age of onset ranges from 6 months to 15 years. Although most are idiopathic in origin, some cases may be induced by drugs (drug reaction). Initially affected sites include paronychia (nail bed inflammation), feet (including pads), face and ears (pinnae). In comparison to the dog, feline pemphigus foliaceus may significantly wax and wane and may have seasonal exacerbations (intercurrent hyper-
sensitivities?). Histopathologic changes are similar to those seen in the dog. Cats with mild disease are treated with prednisolone; moderate or severe disease, oral triamcinolone or dexamethasone. If there is a failure to respond to glucocorticoid therapy or deleterious side effects of steroids are encountered, then chlorambucil or cyclosporine are used. Therapy is usually for life, although a small percentage of cats with PF (approximately 20%) will eventually be able to have their immunosuppressive therapy discontinued after having remission maintained for several months.

**DISCOID LUPUS ERYTHEMATOSUS (DLE)**

DLE often starts at 2-5 years of age and gradually progresses over months or years. The Collie, Shetland Sheepdog, German Shepherd dog and Siberian Husky exhibit a breed predilection for this disease. Lesions are restricted to the face. Progression of lesions of the planum: depigmentation, loss of the normal cobblestone pattern of the planum; inflammation, crusting (usually mild; milder than that seen with pemphigus), erosion, ulceration, loss of supportive nasal cartilage with chronic, severe, deep seated lesions. Variable degrees of pain (more common with more severe disease). Can see significant hemorrhage from very severely affected noses. The bridge of the nose, lip margins and periocular region may also be involved (depigmentation, inflammation, crusting). The medial aspect of the pinna will only occasionally be involved. There is no systemic symptomatology. ANA titers are negative.

The lesions do appear to be photo-aggravated (worse with sun exposure), but this is variable from individual to individual.

Differential diagnoses include mucocutaneous bacterial pyoderma, systemic lupus erythematosus, Idiopathic nasal depigmentation (snow nose), Vitiligo, Pemphigus, Uveodepigmentation Syndrome, Proliferative arteritis, Mycosis fungoides (cutaneous lymphoma)

The diagnosis is often made on a presumptive basis, in light of the history and physical findings. Confirmation based on skin biopsies. Histologic changes include: Mild to moderate vacuolar degeneration of the basal cell layer; apoptotic cells in epidermis (single necrotic cells), usually within the basal cell layer; may be some splitting of the epidermis away from the dermis; thickening of the basement membrane; mild to moderate inflammation at the junction of the epidermis and dermis (interface); may be dense, lichenoid (band -like); made up primarily of lymphocytes, plasma cells and lesser numbers of macrophages, occ. mast cells; usually also perifollicular, periadnexal; pigmentary incontinence (pigment falling out of the epidermis into the dermis) and engulfment by melanophages.

1. May see mucin deposition

**Therapy:**

1. For all manifestations of DLE, sun restriction (between 10:00 AM and 4:00 PM) and the use of topical sunscreens are strongly advocated (e.g. SPF > 30; waterproof - recommended for swimmers, water skiers; babies; apply BID if outdoors all day).
2. Based on a high degree of suspicion for this diagnosis, it is reasonable to treat with more innocuous drugs, without histopathologic confirmation. Drug alternatives would include topical glucocorticoids, topical tacrolimus or oral tetracycline or doxycycline and niacinamide. However, if the problem is severe at onset, or does not appear to be responding to the above medications, it is advisable to biopsy the lesional areas to better define the nature of the problem and prior to starting more potent immunosuppressive therapies (e.g. glucocorticoids or glucocorticoids and azathioprine or cyclosporine).

3. Milder disease can be treated with topical glucocorticoids - beginning with more potent products such as 0.1% betamethasone valerate or 0.5% betamethasone dipropionate or triamcinolone acetonide - some use the product “Panalog” - start with BID administration and once significant improvement noted, gradually reduce the frequency. If lesions do well, try to maintain on twice weekly or less frequent applications. Beware that too frequent maintenance medication may actually cause cutaneous atrophy. In our area (the front range), topical glucocorticoid therapy is often insufficient to control this disease.

4. It has been suggested that mild disease may benefit from oral Vitamin E as an immunomodulator (e.g 400 IU BID or TID). At best, this would be an adjunctive therapy and has not been found to be very beneficial in our area.

5. Tacrolimus (Protopic; Fugisawa) - immunosuppressant that is about 10-100 times as potent as cyclosporine; similar mode of action as cyclosporine. Minimally absorbed. Very well tolerated. Best for mild to moderate cases; apply sparingly to affected areas BID to initiate therapy. Once maximal benefit noted, reduce to once daily, then once every other day. Maintenance is usually once daily or every other day. Quote 60% success in controlling with this medication. No monitoring for systemic complications of this drug is necessary.

6. Tetracycline (for its anti-inflammatory benefit) and niacinamide (B vitamin used for its anti-inflammatory benefit). Tetracycline may be replaced with doxycycline. Used to treat mild to moderate cases (approx 50-60% success). If the lesions are moderate to severe, therapy is usually initiated with glucocorticoids, then maintenance is attempted with tetracycline/niacinamide. Tet./niac. treatment is TID with both drugs initially (500 mg/dog of each; if less than 10 kg, use 250 mg/dog), then reduced to BID and sometimes q24 hrs for long term (indefinite) maintenance therapy. Doxycycline may be initiated on a BID basis (for those folks who cannot treat TID with tetracycline).

7. Glucocorticoid monotherapy (starting at immunosuppressive dosages - 2 mg/kg/day prednisone). Refractory cases are treated with glucocorticoids and azathioprine (must wait at least 3-6 months to assess effects of azathioprine). Those refractory to this combination are treated with cyclosporine.

8. Goal of therapy is to re-epithelialize skin and control inflammation. Some noses may re-pigment. Once repigmentation is achieved, no need for topical sunscreen/sun restriction.