

Management of chronic vesicular dermatitis in an
Egyptian Banded (Snouted) Cobra (*Naja annulifera*).

This report is to present a case of chronic vesicular dermatitis in an Egyptian Banded (Snouted) Cobra (*Naja annulifera*). This snake was treated, despite limitations placed by the owner, using appropriate diagnostics followed by review and changes in its husbandry, medical therapy and follow-up care. The skin and snake progressively healed over almost 3 months and returned to normal.

Vesicular dermatitis is a not infrequent condition found in veterinary and human medicine, and most species of animals have been found to be susceptible to this condition. It is characterized by formation of fluid-filled blisters within the structure of the skin. Histologically, these blisters (vesicles and bullae) are identified by the dermal, epidermal or intraepidermal separation of the skin, forming cutaneous fluid filled vesicles and necrosis of the elevated epidermis.^a These vesicles can be formed by many causes, including infectious, thermal/chemical burns, trauma and autoimmune, and will often rupture, forming erosions and ulcers.^b The open wounds created by these ruptured vesicles then provide a venue for secondary complications such as infections and prolonged healing.^c

Much like an incisional wound, there is both a loss of the immune system function of the epidermis against pathogen invasion as well as loss of fluid regulation function when the damage to the skin is extensive.^d Healing can be

delayed or inhibited as a result of the damage to the dermal vasculature, damage to or loss of the dermis and adnexa, further infections, and introduction of foreign material into the wound.

This condition has been reported in Testudines^e and Squamata.^f In caged snakes, it is possibly one of the most common presentations seen in practice.^c Often, the vesicles are ruptured at the time of examination with the overlying necrotic epidermis removed, and the patient will present with denuded lesions. These lesions may be open and raw, covered by a pseudomembrane of fibrin, or caked with debris from their enclosure. If the scales are still present, they will often appear rough and brown and dilated blood vessels may be visible on adjacent skin and scales. Histologically, these lesions exhibit a loss of most or all of the superficial epidermis with exposed dermal layers and infiltrations of heterophils and monocytes, often with crusts overlying the lesions.

Although it is suggested that bacterial infections are the most common cause of vesicular dermatitis, it has been associated with other etiologies. Therefore other differentials must be considered, including fungal, parasitic and viral infections. Furthermore, it is often found in correlation and/or as a result of suboptimal or inappropriate husbandry.^c

Primary bacterial dermatitis in snakes has not been well reported in the literature. External parasites may be inducing agents, with ticks (*Aponnoma latus*)^f and mites (*Ophionyssus natricus*) suspected as carriers of infections through direct introduction via saliva or as providing an entrance through environmental contamination of the bite wounds.^g Internal parasites such as nematodes, cestodes,

and other helminths all have been found to migrate to subcutaneous tissues and/or infect circulatory and lymphatic systems resulting in cutaneous lesions.^{hij}

As a differential, primary mycotic dermatitis is well reported with multiple infectious agents implicated, including *Penicillium*, *Geotrichium* and *Nannizziopsis*.^k Although fungal dermatitis is rarely seen with the formation of cutaneous vesicles, the common presentation of denuded epithelia in vesicular dermatitis can grossly resemble that of the cutaneous lesions seen in fungal dermatitis.^l

Viral etiologies are not found to specifically cause vesicular dermatitis, but references suggest that there may also be a viral etiology associated with or underlying the bacterial and/or husbandry etiologies identified. Several viral infections in reptiles produce skin lesions (Flavivirus, Poxvirus, Herpesvirus, Papillomavirus), and could be considered as differentials, but there are no specific viral infections yet identified that commonly produce epidermal vesicles in their pathology.^m

Thermal burns are well understood to cause vesicles and blisters, but they are usually localized to a specific area of exposure and are not progressive without continual exposure. Radiation burns have been discussed by practitionersⁿ and suspect “sunburns” have been seen by the author in snakes and lizards overexposed to powerful UV bulbs, but are not documented in the literature. These “sunburns” likely have both UV and thermal components to their pathology, but anecdotally appear to be more common in nocturnal and albino species that may lack sufficient endogenous protection.

Epidermal/dermal separation causing bullae has been reported in cases of

renal disease in snakes.^o Metastatic mineralizations with the formation of dermal fluid pockets have been seen by the author and others.^p These can be differentiated from vesicular dermatitis by both an investigation of biochemical profiles as well as histopathology of both renal and affected tissues.

It is possible and should be considered as a differential that an autoimmune condition may develop in reptiles that cause the separation of the epidermis and the dermis with the subsequent formation of vesicles. Pemphigus diseases are well described in the human and domestic veterinary literature and grossly produce the same lesion as vesicular dermatitis. Histologically, the lesions are similar with dermatoepithelial separation, but easily differentiated. Although not reported in reptiles, this has been suggested in other non-traditional species such as the Korean Fowl^q and in Malayan Tapirs.^r Paraneoplastic syndromes that cause the formation of epidermal/dermal vesicles, again, have been reported in domestic species,^s but have not been reported in reptiles.

The most common unifying etiology in cases of vesicular dermatitis is that of sub-standard husbandry. In all cases of reptile medicine, a thorough knowledge of appropriate housing, lighting, ventilation/humidity, temperatures, night cycle and diet is necessary for the accurate diagnosis of any condition in any species.^t

Environmental moisture is a significant factor in the development of vesicular dermatitis. Many cases are found to have high humidity, wet bedding or even standing water in their enclosures. Ventilation is factors in humidity levels, in that poor air circulation will hold moisture within the enclosure, moisten the bedding without appearing to be wet, and create an environment that is conducive for

bacterial growth. Furthermore, when ventilation is poor, general air quality is generally likewise so. Inhaled contaminants are commonly believed to predispose reptiles to respiratory disease and generally thought to be immunosuppressive.

The enclosure temperature must be considered in any reptilian condition. As reptiles are poikilothermic ectotherms,^u their immune system function is highly dependant on their enclosure temperature, and suboptimal temperatures coupled with predisposing conditions (undigested meal in the stomach, parasite-caused skin wounds, excessive moisture, bacteria-laden bedding, poor air quality, etc) can allow for the development of bacterial infections and septicemia.

Healing of these lesions would follow the four stages of skin healing previously identified in squamates.^v The first stage is that of the initial response to injury, the initiation of inflammatory responses in the injured tissue and the migration of macrophages and heterophils into the wound. These leukocytes provide a local barrier against pathogens, remove debris and damaged tissue and may stimulate fibroblast activation.

Fibroplasia, the migration and generation of mesodermal cells within the wound dominate the second stage. This, coupled with angiogenesis and the formation of collagen, provides a structural bridge to the skin defect. To restore the integrity of the damaged skin and subsequently decrease fluid loss and protect against secondary pathogenic invasion, the surface of the defect is filled with fibrin. This repair is a migratory process, starting at the wound margins across the defect with the deeper layers (hypodermis) being repaired last.

The third stage of squamate wound healing involves the restoration of the epithelial layer, and is shown to be very similar to how it occurs in mammals.^w The epithelial cells migrate from the wound edges across the basement membrane of fibrin and granulation tissue, recently formed by the fibroblastic dermal layer.

The last stage of healing is the growth, reorganization and maturation of the epithelial layer into a skin layer nearly identical to that of tissue adjacent to the damaged area. Ordered stratification and keratinization of the epidermis and a restructuring of the inner generation layers occur at this point.

All of these stages of healing are occurring concurrently with normal ecdysis although are not reported to be in synchrony with the shed cycle. When the reptile is at its resting phase within the epithelial cycle cell, the generation of epithelial cells all but stops and increases during the renewal phases.^x Wound regeneration rates have been found to mirror that of normal skin and final maturation and differentiation is not complete until both the structure and function of the regenerated dermis and epidermis match that of the rest of the reptile.^y

There also is hormonal control of the regeneration of squamate skin. In lizards, it has been found that increased thyroid hormone is a stimulator of the regenerative phase and ecdysis, whereas increased thyroid hormone(s) promotes the resting phase and decreased serum thyroid hormone levels may bring on the renewal phase in snakes.^{z aa bb} Another assessment of the role of thyroid hormones in the ecdysis cycle of snakes suggests that snakes epidermal regeneration is accelerated by hyperthyroidism.^{cc} These countering findings indicate that much

more study is needed, but it is agreed that many factors can affect thyroid levels, including systemic health and seasonal variation.^{dd}

Treatment of vesicular dermatitis requires first identification of any deficiencies or incongruity in the patient's husbandry and thus, a complete history is needed. If the clinician is familiar with the correct husbandry for that species, it can be simply compared to the description provided by the owner. In less common species, research to identify the species' natural history and range will provide clues to possible husbandry factors, and there are well-researched published refereed articles on the care and keeping of hundreds of species of snakes, lizards and chelonians. Consulting with zookeepers, professional breeders and other herpetological veterinarians familiar with the species are very good resources. Finally, one may use the web as a resource for identifying appropriate husbandry, but this must be used with great caution. Much of the content available on the internet is that of opinion and has not been assessed for accuracy, and thus may be fraught with errors.^{ee}

A full physical exam needs to be conducted to assess the overall condition of the patient. The overall physical condition should be considered as well as other observable physiological parameters and conditions that may be present. The skin itself can then be examined to assess its condition. Lesions need to be identified and recorded for size, approximate depth of ulceration and/or vesicles, degree of erythema and other superficial vascular changes, and the scope of the disease over the patient.

Diagnosing the specific condition and ruling in or out differentials requires a biochemical profile and complete blood count, skin biopsies (that include both areas of lesion and normal skin) with histopathological analysis, and bacterial and fungal cultures of vesicular fluid and/or deep skin scrapes after the superficial crusts and debris have been removed. A blood culture is also indicated, as the vesicular fluid is often sterile and/or organisms isolated from inside the lesion may be secondary or contaminants, whereas the causative agent can often be identified as a septicemia.^{ff}

Correcting deficiencies in the husbandry is paramount to a successful treatment in that if the husbandry is inappropriate, the recovery will be temporary, at best, and at worst, the patient will not recover.^{gg} Specifically this should include, at least temporarily, changing the environment to a solid, absorptive, dry substrate, such as paper towels, cloth layers or unprinted newspaper, frequent (daily or when soiled, which ever is more frequent) bedding changes, lowering ambient humidity/increasing ventilation and keeping the animal in the higher end of the preferred optimal temperature zone (POTZ) for that species.^{hh} Continued feeding should be part of therapy as all animals require a good plane of nutrition to maintain both systemic and immune system health; some individuals will require assisted feeding to continue caloric intake.

Blood biochemical and cytological analysis is used to identify underlying or predisposing conditions, such as hepatic, renal, or other metabolic diseases. If these are identified, part of the treatment plan must include addressing and working to correct these issues. Further diagnostics, such as tissue biopsies, viral testing, serum vitamin levels or other specific tests will need to be considered on a case-by-

case basis, depending on both the specific presentation of the species as well as the results of the other diagnostic testing performed.

Specific treatment for vesicular dermatitis involves both a systemic treatment plan as well as a dermal treatment plan. Antimicrobial therapy should be based both on the results of the cultures and sensitivities as well as the species and overall health of the patient involved should be considered; for example, antibiotics that concentrate in the kidneys with a risk of renal damage should not be used in arid-environment species, nor should medications that require hepatic processing should be used in patients that have indications of hepatic disease.ⁱⁱ

Topical treatment is necessary to control the lesions from further spreading, as well as promote healing of the primary wounds. Removing all debris from the surface of the wounds followed by cleaning with a disinfectant, such as povidone iodine or chlorhexidine, should be performed regularly. This therapy will promote healing by reducing the degree of superficial infection as well as remove any material that might be inhibiting normal migration of regenerating tissues. This cleaning should be done daily to remove any crusts/debris that may build up from material in the enclosure or from exudate produced by the wound. After cleaning, covering the wound has been found to be beneficial with an adhesive bandage product (such as Tegaderm), a clear plastic drape,ⁱⁱ or a liquid “bandage” product (such as “NewSkin”). Choice of the bandage material used depends on the clinician’s choice, the location and extensiveness of the wound(s) being covered, and the species/behavior patterns of the patient. This covering will prevent further material from adhering to the wound, prevent additional secondary

contamination/infection, and promote healing by stopping desiccation of new tissue. Additionally, these bandage products reduce systemic fluid loss until the impermeable epidermal layers have regenerated.

Once the inciting cause(s) has been controlled and recovery begins, it generally takes several shed cycles for the skin to completely regenerate. As discussed above, although migration of fibroblasts is a continual, gradual process, the restoration of the α and β layers of the skin is discontinuous and coordinates itself to the rest and regeneration cycles of ecdysis. Therefore, in a properly managed case, with each shed there will be seen more “normal” skin surrounding the gradually shrinking lesions.

Prognosis for these cases is variable and depends on several factors: 1) Severity of the condition, thus related to chronicity, 2) Compliance of the owner, as these cases require long-term management and care generally performed at the owner’s site, 3) Correction of the husbandry to a more optimal state, and 4) Identification and appropriate treatment of additional or underlying/predisposing health issues.

Clinical Report:

The patient, a 5.2 kg, approximately 21 year old intact probed male banded cobra (*Naja annulifera*), presented for an estimated 5 month history of variably sized rough debris-covered tan to brown lesions on the dorsal and lateral skin at random locations along the length of the neck, body and tail. The owner had noted them developing originally on the mid-body and that they developed and grew slowly while additional lesions formed elsewhere. There had been no change noted

in the patient's activity level or appetite since prior to the onset of disease.

The owner's collection was a mix population of venomous (all reportedly venomoid) and non-venomous reptiles, including members of many different taxonomic groups (Squamates (snakes and lizards), Chelonia and Crocodylia). All animals of different species were housed individually, but in close proximity to each other. Hired staff attended to the general care and cleaning of most of the animals, but many of the animals were provided with sub-optimal husbandry. Despite this snake having no specific history of disease, the collection had a recent (one-year prior) history of *Ophionyssus* mite infestation, some animals had been diagnosed with *Cryptosporidium* infections, and many individuals had been found to have one or more of a variety of protozoan and helminth gastrointestinal parasitic infections. At the current time, however, no mites had been observed within the collection and all animals determined to have internal parasites either had been or were currently undergoing appropriate therapy.

The snake was housed individually. The enclosure had been used exclusively for this animal for between five and ten years, was a custom-made paint-covered wood cage approximately 70 cm wide, 200 cm long and 70 cm tall, elevated about 1 meter off the floor with two glass doors that were approximately 80% of the front surface. The room was kept at a constant 25° C and there was a warmer area within the cage at 27-28° C with heat provided by a commercial heat pad attached to the underside of one end of the cage. Ventilation was passive and provided by four-2 cm drilled holes at each end of the cage in the upper corners. A single 1-m florescent light fixture was mounted to the inside top of the cage and was turned off

and on manually every 12-14 hours. The substrate within the cage was commercially available chopped aspen bedding and the only furniture within the cage was a 30 cm diameter ceramic bowl containing water. The bedding was “spot-cleaned” when soiled, every 7 to 10 days and changed about monthly. The water was changed weekly and the bowl was cleaned at that time. The patient was fed one or two frozen/thawed medium to large rats purchased from a large commercial rodent breeder about every 7-10 days.

The patient had been purchased as a 60-70 cm wild-caught juvenile by the owner approximately 20 years ago and had undergone surgery to remove the venom glands at that time by an unknown provider. The owner recalls that the patient had also been “treated for parasites” at the time of purchase, but had no recollection of the drug used, nor the dose or frequency. Per the owner, no other treatment had ever been administered to the patient nor had the patient any history of illness noted.

On presentation, the patient was bright, alert and responsive and was actively moving around the semi-transparent plastic tub, where he was initially visually examined. His surface temperature was measured as 22° C using a laser directed thermal measuring device^{kk} calibrated to 0.1° C at 100 mm. For a thorough examination, the snake was controlled and removed from the transport container by the owner using initially two 1-meter snake hooks, then only using one hook and the patient coaxed into a 1 m x 75 mm clear acrylic tube for further restraint. The open end of the tube was fitted with a home-made adapter so that after the patient was well within the tube, the tube was attached to an anesthetic machine coupled to a

Mapleson-D circuit (non-rebreather) and isoflurane^{ll} was administered at 5% with a 2 l/min oxygen flow. The patient became very active and attempted to back out of the tube, but was able to be restrained for sedation.

After about 5-7 minutes, the patient was sufficiently sedated for further examination and was placed on a heated table at 32° C while anesthesia was continued. A Doppler probe^{mm} was taped to the area of the body just cranial to the heart for monitoring. The lesions were found to be random but extensive over the dorsum from the base of the head to nearly the vent ranging from 0.5 to 15 cm in diameter with the largest lesions at the midbody. The dorsal lesions were of varying shape and had irregular margins. Superficial crusts of dried exudative material were on all of the lesions noted on the dorsum. In all of the larger lesions (>13 mm), vesicular-type structures were seen circumferential to the crusts with the epidermis elevated from underlying suspected dermal tissue and a small amount of low-viscosity fluid within. The crusts were easily peeled from the surface of the lesion, revealing exposed subepidermal tissue lacking scales that was hyperemic and raw in nature. Normal but faded pigmentation appeared to be present, suggesting that the dermis was intact and that the lesions were partial, rather than full, thickness. Additionally, there were two areas of the ventral scutes that were similarly affected, each about 3 cm wide with one affecting 3 scutes and the other 4 scutes. The ventral lesions were primarily marked by discoloration of the scutes and mild dilated blood vessels, edema, and hyperemia peripheral to the lesions; no open wounds or crusts were present.

The remainder of the examination was unremarkable. There were no

abnormal swellings or masses palpated within the coelom. The vent was clean with no lesions although the patient expressed a large amount of fecal, urate and scent gland material. An oral examination was performed by sliding the head of the patient to the proximal (relative to the anesthetic machine) end of the acrylic tube and opening using wooden tongue depressors and viewed with a compact light source.^{no} No abnormalities were noted within the oral cavity.

The owner approved collection of samples for further investigation. The base of the tail was cleaned with chlorhexidine^{oo} prior to phlebotomy. Blood was drawn from the ventral tail vein using a 3 cc syringe and 27-gauge needle with a packed cell volume and total solids quantification by refractometer (PCV/TS) processed in-house and a complete blood count/full reptile serum chemistry was sent to a local reference lab for analysis. Fluid was aspirated with a 0.5 cc tuberculin syringe using a 29 g needle from one of the larger vesicles and spread on a slide and stained with a modified Wright's stain^{pp} for immediate review. The PCV was measured at 33% and the total solids was found to be 9.0 g/dl. A mild red blood cell contamination with a large amount of fine granular basophilic ground material was found on the fluid cytology. There were few to rare heterophils present and no bacteria or fungal material was observed.

The results of the complete blood count and serum chemistry are listed in table 1.

TABLE 1:

Complete Blood Count:	Patient	Normal values, Naja naja ⁹⁹
WBC:	15,200/ul	7738 +/- 4951
Heterophil:	1060/ul 7%	627 +/-355/ ul
Lymphocytes:	9730/ul 64%	5218 +/-4246/ ul
Monocytes:	4410/ul 29%	48 u/l (no std dev reported)
Eosinophils	N/R	N/R
Basophils:	N/R	106 +/- 58/ ul
Azurophils:	N/R	2044 +/-862/ ul
PCV:	34%	23.3 +/- 9.1%

Pathologist comments:

Thrombocyte estimate is normal. RBC morphology is normal. WBC estimated from slide. 0-5 lysed cells per HPF. Excellent quality.

Serum Chemistry:

Glucose:	115 mg/dl	30 +/- 14 mg/dl
BUN:	<0.5 mg/dl	3 +/- 1 mg/dl
Sodium:	171 meq/l	162 +/- 4 meq/l
Potassium:	5.3 meq/l	5.6 +/- 1/6 meq/l
Na/K ration:	32	N/R
Chloride:	120 meq/l	125 +/- 11 meq/l
Calcium:	19.4 mg/dl	16.9 +/- 1.4 mg/dl
Phosphorus:	4.7 mg/dl	3.6 +/- 0.8 mg/dl
Total protein:	8.9 g/dl	5.8 +/- 1.1 g/dl
Albumen:	3.9 g/dl	2.5 +/- 0.5 g/dl
Globulin:	5.0 g/dl	3.4 +/- 0.8 g/dl
Alb/Glob ratio:	0.8	N/R
GGT:	12 u/l	5 u/l (no std dev reported)
AST:	30 u/l	17 +/- 25 u/l
CK:	712 u/l	635 +/- 527 u/l
Cholesterol:	286 mg/dl	384 +/- 167 mg/dl
Amylase:	1429 u/l	N/R
Uric Acid:	3.9 mg/dl	3.9 +/- 3.8 mg/dl
Bile Acids:	80 umol/l	N/R
Ca/P ratio:	4.1	N/R
Triglycerides:	400 mg/dl	22 +/- 4 mg/dl

Biopsy samples of the lesions were obtained. Although the snake was well sedated, it was not in a surgical plane of anesthesia. To reach a level of surgical anesthesia, propofol[®] was calculated at 10 mg/kg and then given to effect via a 25 g butterfly catheter, intracardiac. The site where the Doppler probe had been taped was surgically prepped, the heart was physically isolated and stabilized and the needle was inserted into to the area determined to be the heart base. 5 ml of blood was first collected and added to a blood culture vial, and the syringe was replaced by one containing propofol. The intracardiac location was confirmed by aspiration of a small amount of blood into the catheter and 2 ml was slowly infused. The tail was gently pinched about 60 seconds post administration and a small response was elicited. Aspiration of blood was repeated for confirmation of needle location followed by the infusion of 1 ml additional propofol. Another minute passed and a repeat tail pinch was performed. The patient did not respond so it was deemed to be at a sufficient plane of anesthesia. A total of 3 ml of propofol was administered. The Doppler probe was replaced for further monitoring. Isoflurane concentration was reduced to 2.5%. The patient continued to breathe spontaneously and very little change was noted in heart rate throughout the entire procedure.

A portion of a larger lesion was selected for biopsy. The crust over the lesions were initially left intact to preserve any bacteria present within the lesion, but the periphery of the lesion and surrounding skin was cleaned using standard technique and povidone-iodine surgical scrub^{ss}. The area was draped, effort was made not to remove the crust and an elliptical approximately 5mm x 10mm section of full-

thickness skin was taken by sharp incision using curved iris scissors, including normal, marginal and ulcerated skin. The lesion was carefully prepped again, using only povidone iodine surgical scrub soaked into sterile gauze applied to the entire lesion, taking care not to contaminate the surgical wound. The wound was closed with 3-0 glycomer 631 monofilament synthetic absorbable sutures^{tt} suture in an interrupted horizontal mattress pattern; two sutures were required to close the wound. The procedure was repeated twice more in two separate areas of skin. The biopsy samples were all cut into two portions: One piece of the first two samples was placed in formalin and the other placed into a microbiology transport tube. The third biopsy sample had each piece placed in either of the two microbiology transport tubes.

At 22 minutes of gas anesthesia and the point that the third biopsy site was selected and prepped, the isoflurane vaporizer was turned off and the patient continued to breathe 100% oxygen. The remainder of the lesions were cleaned with povidone-iodine surgical scrub and allowed to dry. Meloxicam^{uu} was administered for post-operative pain at 0.2 mg/kg, subcutaneously to the middle third of the body, at least 15 cm from any surgical wound and in an area of healthy skin. The snake was removed from oxygen once a tail reflex returned, and once a small amount of conscious motion was observed, was returned to its transport container for the remainder of the recovery and the patient was discharged approximately one hour later.

Discharge instructions were as follows: The patient to be kept only on clean, dry newspaper and changed frequently when soiled or wet. The water bowl to be

reduced in size so that the snake could drink, but not soak within it. Water was to be changed daily. Cage temperatures to continue as previously, ensuring that there was a basking area of 32-34 C. All skin lesions were to be cleaned with dilute (1:5) iodine solution daily and allowed to dry naturally. As no bacterial agents were identified on microscopy, no medical therapy would be initiated until histopathology results were returned.

The fixed samples were submitted for histopathology and the microbiology transport tubes containing the tissue samples were frozen at the owner's request for later submission. The blood culture was declined for submission. A fecal float and direct and an acid fast staining^{vv} of a fecal cytology were performed in-house after the patient left. The fecal floatation and wet-mount cytology did not identify any parasites, and the acid-fast cytology of a fecal sample did not identify any *Cryptosporidium* organisms.

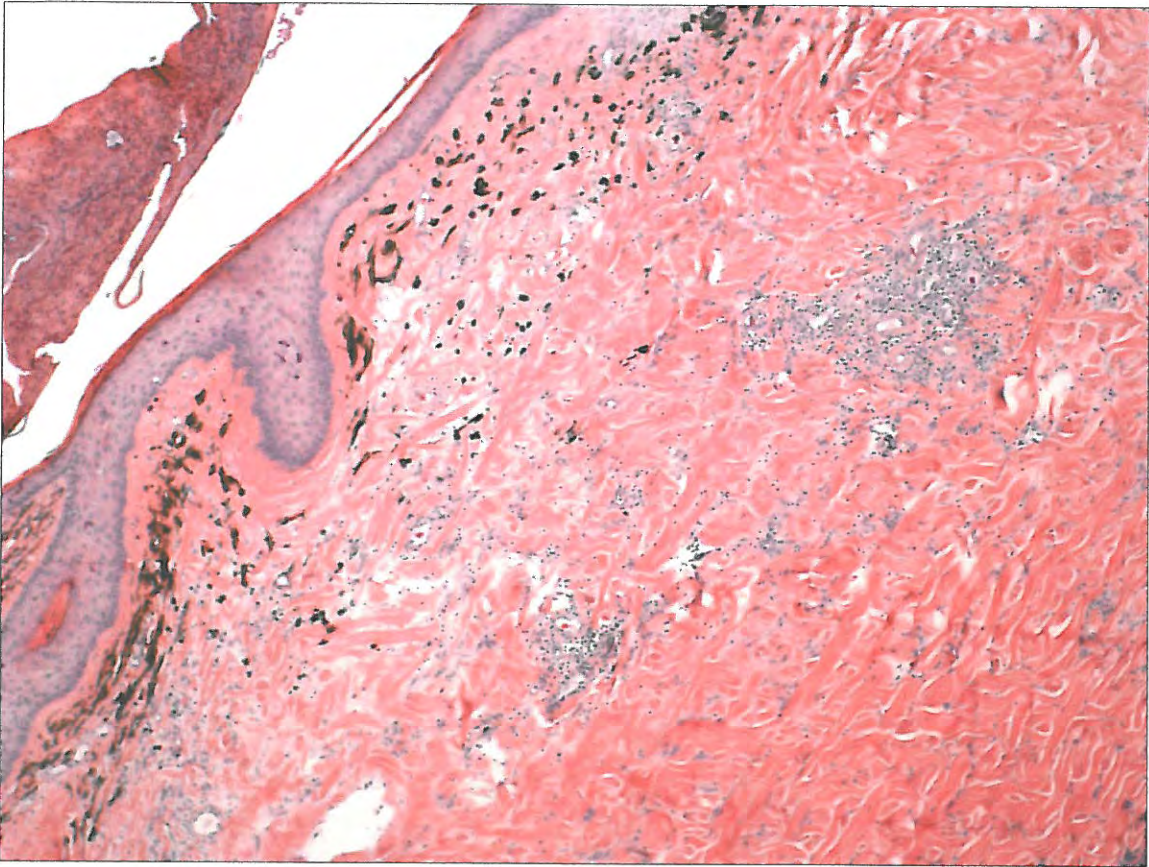
Histopathological examination of the biopsies found focally extensive erosive and ulcerative acute to subacute dermatitis with subacute perivascular dermatitis. Only small fragments of the overlying stratified squamous epithelium was still adhered to the dermis, with the rest being an ulcerative surface, denuded down to the superficial dermis. A variably thick serocellular inflammatory exudate overlay the remaining keratin. Small coccoid-shaped bacteria were found within the inflammatory exudate. It was undetermined based on these histopathological results whether or not these bacteria were responsible for the lesions observed.

Furthermore, there was a significant mixed inflammatory cell infiltrate in the skin, with heterophils transmigrating across the stratified squamous epithelium.

Higher numbers of heterophils are observed within the ulcerated sections and within the superficial dermis lymphocytes, plasma cells and heterophils are surrounding blood vessels.

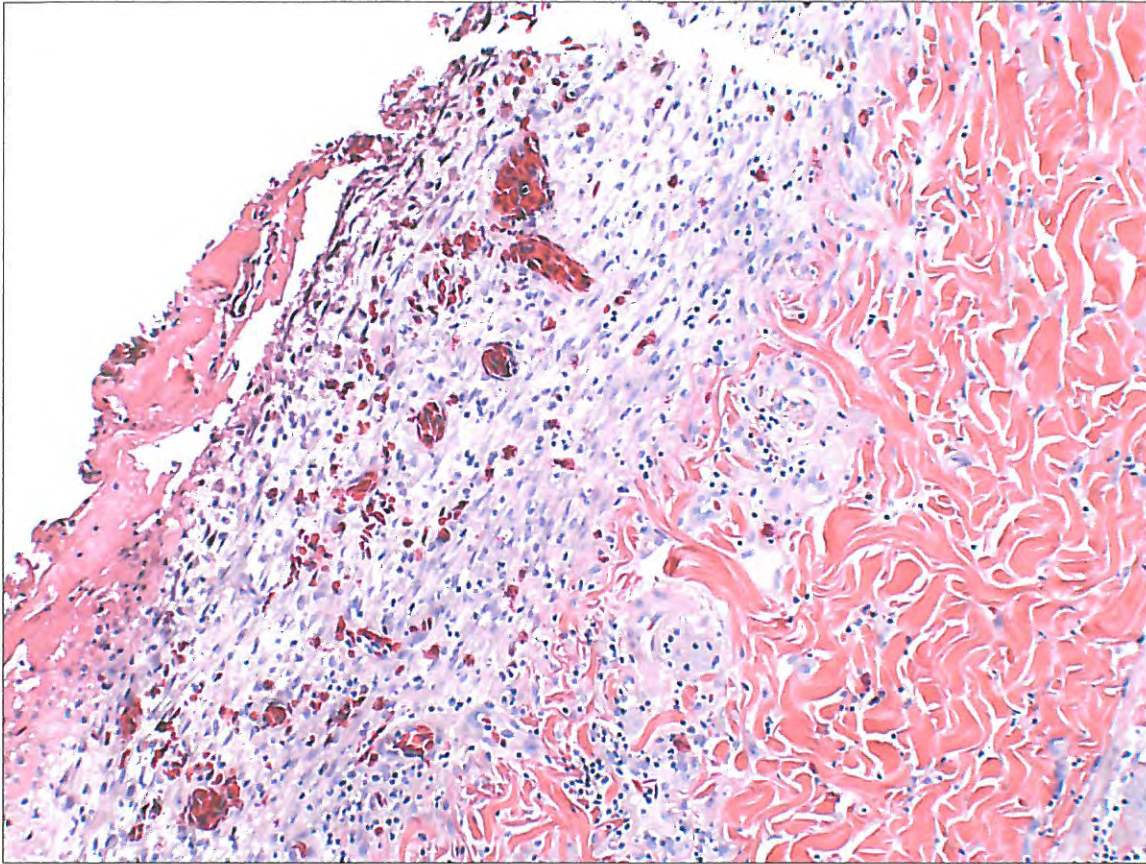
Figures 1 and 2 support the histopathological findings.

FIGURE 1:



This section is supporting an intact epithelium with an overlying inflammatory crust (upper left). In the dermis there are nodular proliferations of perivascular inflammatory cells. Image taken through a 4X objective.

FIGURE 2:



This is a section of ulcerative dermatitis with a thin adherent inflammatory exudate. Image taken through 10X objective.

As there was no indication of neoplasia but good indication of an inflammatory reaction and bacterial infection, the owner was contacted to discuss the findings and for permission to submit the frozen samples for bacterial and fungal cultures and to start the patient on antibiotics. Initiation of antibiotic therapy was approved. Cefotaxime^{ww} was prescribed at 20 mg/kg SQ q 24 h for 10 days. aerobic bacterial culture was approved 6 days later on day 16.

The culture found multiple species of potential pathogens. The culture and sensitivity results are listed on Table 2.

TABLE 2:

Organism #1

Pseudomonas aeruginosa

LIGHT GROWTH

Organism #2 *Escherichia Coli*

LIGHT GROWTH

Organism # 3

Coagulase negative *Staphylococcus* spp.

LIGHT GROWTH

Organism # 4

Enterococcus species

AVIAN/REPTILE KB SENSITIVITY	#1	#2	#3
Amikacin	S	S	S
Claforan (cefotaxime)	I	S	S
Ceftazidime	S	S	I
Naxcel (ceftiofur)	R	S	S
Cephalexin	R	I	S
Clavamox (amoxi-clav)	R	S	S
Doxycycline	R	S	S
Enrofloxacin	S	S	S
Orbifloxacin	S	S	S
Piperacil (piperacillin)	S	S	S
Tetracycline	R	S	S

Timentin(ticarcillin-clavulanic)	S	S	S
TMP/Sulfa	R	S	S
ENTEROCOCCUS SENSITIVITY PANEL		#4	
Ampicillin	S		
Amoxicillin	S		
Zithromax (azithromycin)	R		
Chloramphenicol	S		
Biaxin (clarithromycin)	R		
Difloxacin	D N R		
Doxycycline	S		
Enrofloxacin	S		
Erythromycin	R		
Gentamicin (High Conc.)	S		
Marbofloxacin	I		
Streptomycin (High Conc.)	S		

Despite sensitivity of two of the identified bacteria to cefotaxime, there was no significant improvement in the condition of the lesions. It was advised to change the antibiotics to piperacillin/tazobactam^{xx} to provide the greatest coverage of sensitivity to all organisms identified. The owner declined using this medication, so the patient was prescribed ceftazidime^{yy} at 20 mg/kg SQ q72 h for 28 days. Despite stressing to the owner that overlapping of antibiotic therapy was strongly recommended, the owner did not start administering ceftazidime until 28 days after the initial visit, 6 days after cessation of the cefotaxime.

Although the owner was unwilling to bring the patient back in for another examination, a site visit to reevaluate the condition was made on day 46, 18 days after starting the ceftazidime. The majority of the crusts and lesions were healing, particularly at the biopsy sites, which appeared to be healing faster than many of the other lesions, and there appeared to be no new vesicles forming. As the suture lines appeared to be well healed, and the patient had shed once since surgery and was currently about to shed again, the sutures were removed.

Unfortunately, the husbandry for the animal had not been optimized. The patient, instead of being returned to his regular cage and kept as instructed, had been kept since his return in the large plastic transport container he had been brought to the hospital in when the biopsies were performed. Although the bedding had been changed out to newspaper, and a three-inch screened vent had been installed at each end for ventilation, he had been offered water once weekly and was being kept at ambient temperature (approximately 23-24° C) with no basking area

provided. The wounds had been cleaned with iodine every 4 to 5 days. Feeding had been continued at an interval of every 5-7 days and the owner had noted no changes in appetite. The lesion at the base of the head was larger and worse than previously seen, despite improvement in the lesions on the rest of the body.

Instructions were given to improve the husbandry of the patient. The owner was instructed to put the snake back in its prior cage or a comparable cage, keep the bedding as newspaper or equivalent, increase the temperatures so that the basking area was approximately 32-35° C, with the cool end of the cage no less than 25° C and provide a night heat source so that cage temperature would maintain between 25-28° C. Water was to be supplied every 2 to 3 days as a flat dish large enough for the patient to drink from, but not large or deep enough for the patient to soak within.

The previous care instructions were reiterated to the owner and plans were made to recheck the animal again in approximately 10 days as well as determine if the patient should continue on antibiotic therapy. This recheck was delayed at the request of the owner and the owner did not immediately reschedule.

At day 67 post initial exam, an on-site recheck was made, and the husbandry was found to be corrected as instructed. The snake had been transferred to a larger temporary cage with better ventilation and a higher heat range and basking area. The patient was reported to have been spending much of the time in the basking area, and had shed once again since last seen. All of the lesions on the body were found to be covered in normal, healthy epidermis, and the locations of the lesions on the ventrum were unable to be identified. The lesion at the base of the head was

still present, but dramatically reduced in size and showing general healing and improvement. The owner reported that he was still cleaning all the lesions daily, and felt that the delayed healing of the wounds on the neck were likely iatrogenically caused by restraint of the patient during the daily cleaning. Upon close examination of the affected skin and the observation of mild trauma occurring while the owner was holding the patient at that time, it was concurred the current lesions were had an iatrogenic etiology. The care instructions were changed to only clean the active lesions every other day and minimize restraint.

The patient's cage was reviewed at this examination. Two primary changes to the enclosure were instructed:

First, increase the ventilation and air circulation of the enclosure: An engineer was consulted^{zz} and the advice was given that 15 square cm of ventilation should be made per 0.1 square meter of floor surface area for convective passive ventilation in a small enclosure. As the cage had approximately 1.4 square meters of floor area, this calculated out to 210 square cm of ventilation. Each of the holes previously drilled had an area of approximately 6 square cm, so this calculated out to approximately 56 square cm. Another 150 square cm needed to be installed, and it would be best if split between the ends to provide cross ventilation. Either as a replacement for some of the ventilation area or as an adjunct to passive ventilation, installing active ventilation (a fan) would be ideal to increase air exchange as it would allow for better removal of odors, moisture and excess heat.

Second, increased the temperature range available to the patient: The historical husbandry of the snake did not show that he was not able to

thermoregulate into temperatures that approximated the upper end of his POTZ. A recommendation was made to provide a basking area in the 30-34° C range, while allowing the other end of his cage to remain lower in the 25° C range. The concern was noted that excessive heat could concentrate in his cage; increasing the ventilation, especially providing active ventilation, would alleviate this concern.

A final recheck occurred at day 98 and there were only very small skin lesions at the base of the head to be identified on the patient. Based on discussions with the owner, this was likely secondary to trauma caused by handling each day as the owner wore abrasive "bite-proof" gloves and held the head to prevent bites. Blood was taken and the results were obtained.

The results of the complete blood count and serum chemistry are listed on table 3.

TABLE 3:

Complete Blood Count: Patient Normal values, Naja naja⁹⁹

WBC:	10,100/ul	7738 +/- 4951
Heterophil:	210/ul 2%	627 +/-355/ ul
Lymphocytes:	7980/ul 79%	5218 +/-4246/ ul
Monocytes:	400/ul 4%	48 u/l (no std dev reported)
Eosinophils	100/ul 1%	N/R
Basophils:	N/R	106 +/- 58/ ul
Azurophils:	1410/ul 14%	2044 +/-862/ ul
PCV:	33%	23.3 +/- 9.1%

Pathologist's Comments:

Thrombocyte estimate is adequate.
 0-5 Lysed cells/50 X. Excellent quality.
 7 immature erythrocytes/100 leukocytes.
 Rare phagocytic monocytes noted.
 RBC - WNL
 Lymphocyte count is within normal limits.
 While azurophilia/monocytosis has improved, it
 is still present and cells appear reactive.

Serum Chemistry:

Glucose:	64 mg/dl	30 +/- 14 mg/dl
BUN:	<0.5 mg/dl	3 +/- 1 mg/dl
Sodium:	163 meq/l	162 +/- 4 meq/l
Potassium:	5.3 meq/l	5.6 +/- 1/6 meq/l
Na/K ration:	31	N/R
Chloride:	124 meq/l	125 +/- 11 meq/l
Calcium:	21.8 mg/dl	16.9 +/- 1.4 mg/dl
Phosphorus:	4.0 mg/dl	3.6 +/- 0.8 mg/dl
Total protein:	7.9 g/dl	5.8 +/- 1.1 g/dl
Albumen:	3.4 g/dl	2.5 +/- 0.5 g/dl
Globulin:	4.5 g/dl	3.4 +/- 0.8 g/dl
Alb/Glob ratio:	0.8	N/R
GGT:	3 u/l	5 u/l (no std dev reported)
AST:	122 u/l	17 +/- 25 u/l
CK:	738 u/l	635 +/- 527 u/l
Cholesterol:	258 mg/dl	384 +/- 167 mg/dl

Amylase:	1180 u/l	N/R
Uric Acid:	1.1 mg/dl	3.9 +/- 3.8 mg/dl
Bile Acids:	10 umol/l	N/R
Ca/P ratio:	5.5	N/R
Triglycerides:	28 mg/dl	22 +/- 4 mg/dl

The blood analyses were deemed greatly improved and the lesions on the base of the head were superficial and not indicative of further infection. It was decided that further, regular forced handling of the patient would likely cause further trauma and delay final healing further than necessary. The animal was cleared of further treatment for the skin. The owner reported that the suggested modifications were made to the snake's enclosure and the patient was returned to his prior cage.

Discussion:

Vesicular dermatitis is a very common finding in reptiles that are kept in suboptimal husbandry, despite this animal being kept in husbandry that should have a relatively low predisposition to this condition.

As the patient was kept in relatively correct husbandry for the species (dry enclosure, moderate general temperatures, good frequency of feeding), a specific cause for this case was not immediately apparent. It is possible, even likely, that at least part of the inciting cause for the condition seen was poor quality husbandry, based on history both of the animal as well as the facility. As there was poor ventilation and heat in the animal's cage, these should be considered as a factor although it must be asked why such a condition did not occur prior in the five-to-ten years that this animal had been living in that enclosure.

Although bacterial infections are the most common cause of infectious dermatitis in reptiles,^{aaa} other etiologies had to be considered since there were no bacteria seen on initial cytologies. Ideally, an anaerobic and aerobic culture would have been submitted at the time of presentation, but these tests were initially

declined. Anticipating possible outcomes, however, biopsy samples were set aside in transport media and frozen with the intent to convince the owner of their diagnostic necessity. Although freezing and later submission is not ideal in that some pathogens may be destroyed in the freezing process, it was considered to still be effective in a diagnostic process in that the most common bacteria, most likely to be the primary pathogens, will be preserved because of sheer numbers of bacteria present.

The literature supports the necessity of a blood culture as appropriate diagnostics for cases of vesicular dermatitis as septicemia is often correlated to this condition.^{ff} Blood was initially collected for this purpose but was specifically declined by the owner, and, as blood cultures are not known to be stable with freezing, the sample was discarded. After the histopathology results were returned and indicated a dermal bacterial infection, the quandary was faced to recommend either a bacterial culture of the biopsy samples or collect blood again for a blood culture as the owner was not inclined to perform both tests (which would have been more ideal). Based on that recovery would require the rapid resolution of the skin wounds (preventing reinfection, water loss, conditions secondary to the pain of open dermal wounds), and that blood culture can produce false negative results more frequently than other culture types, the decision was made to recommend culturing of the biopsy samples for determining antibiotic choice.

Fungal dermatitis is commonly reported in reptiles, although vesicle formation is not the most common presentation. Hyperkeratosis and granulomatous inflammation is a more common finding in mycotic infections, and would have been

expected to be seen, if present, on the histopathological samples.

A viral etiology may have been possible in this case, although viral vesicular dermatitis has not been reported in reptiles. If this case had not responded to antibacterial therapy or soon recurred, it would have been appropriate to test further for presence of a viral infection. Furthermore, there was no indication of a prominent lymphocytic response in the biopsies taken in the complete blood count performed. No cytoplasmic or intranuclear inclusions were noted on the histopathology, but this should not be considered definitive for lack of a viral etiology.

Neoplastic and paraneoplastic conditions causing vesicular dermatitis have been reported in mammals, but have not been identified or reported in reptiles. Again, no suggestions of these types of conditions were noted on histopathology.

Physical trauma is a likely predisposing factor in this case. An undetected or unreported mite infestation is suspected to be the underlying etiology. As noted, there had been an infestation of snake mites (identified as *Ophionyssus natricus* on another snake by the author) found 12 months prior within the same collection, but none were reportedly seen on this snake. The author had not examined this individual at that time. As the owner had reportedly treated the entire collection for mites over the last year, it is entirely likely that an infestation in this patient had occurred but was not seen. The bites caused by this possible mite infestation could very easily cause the penetrating wounds necessary to initiate this case of vesicular dermatitis.

A compounding problem in this case is that of it being a chronic condition. As

per the owner, this patient had been showing signs of skin disease for several months and treatment had not been sought nor changes made in its husbandry during that period. The predominantly heterophilic response observed in the histopathology suggests that the wounds were later in healing, also reflecting the effects of the bacterial infection.

The histopathology found acute and subacute pathology in the skin indicating that although the lesions had been present for several months that the process was an active, spreading condition and that the oldest areas of disease were not well represented in the sections submitted. There is also the possibility that early lesions had healed, but that is not substantiated by the presence of scarred areas seen on the initial physical exam, while scarred skin was seen on follow-up exams in areas that previously had lesions.

This patient, being of a venomous species, created additional challenges in the diagnostics and treatments.^{bbb} Although this snake was reportedly venomoid, it is the author's policy to treat all venomous species equally, whether venomoid or not. This meant that, per hospital policy, all procedures in this patient are either performed on-site at the owner's facility or when the hospital is empty (in "off-hours") and that there are no personnel present that are not trained in the handling of venomous species. The author's policy also requires that venomous patients be anesthetized prior to examination and throughout any examination and/or procedures performed.

Blood analysis (complete blood counts and serum chemistries) in reptiles and especially in cases of patients that are going to be/are anesthetized and/or

undergoing immediate surgical procedures are procedurally to be run in-house to have results prior to anesthesia events. However, as the patient must be anesthetized prior to examination and blood collection, and considering that the author was the only medical personnel monitoring the patient, it was not prudent and safe to leave the anesthetized patient unattended. Furthermore, the clinical pathologist requested at the local reference lab has both extensive training and experience with reptile blood cytology, and thus excellent results were expected. No reference blood values were able to be found for this species, but since *Naja annulifera* is considered closely related to *Naja naja* and only relatively recently has been taxonomically separated from this species^{ccc}, using ISIS values available for *N. naja* is the most appropriate comparison.

The complete blood count results identified markers for inflammation and infection. The patient was initially found to have a moderate leukocytosis with high normal to mildly elevated heterophils and lymphocytes and a marked increase in monocyte counts. A mild polycythemia was also present, and it is likely that when corrected for the dehydration interpreted in the serum chemistries, only the leukocytosis secondary to a monocytosis would remain. This monocytosis is interpreted as a marker for the chronic condition identified.^{ddd}

The patient's serum chemistries suggested elevated triglycerides, elevated gamma-glutamyltransferase (GGT), hyperglycemia and hyperproteinemia. Although reference ranges are reported for triglycerides for *N. naja*, there are no applicable reports validating the significance of an elevated value. In mammals and/or birds, elevated triglycerides are associated with a high fat or carbohydrate diet, renal

disease, diabetes, pancreatitis and hypothyroidism. A recent meal can also cause an elevated serum triglyceride level. Since no change in type or frequency of feeding had been reported and since the patient had not been fed for at least 3 days prior to the blood collection, this may be a variant of normal or within normal for this species. As the *N. naja* ISIS value for GGT was based on a single collection from a single individual, the interpretation of this patient's measured levels are not deemed to be significant. Furthermore, upon examination of reference values for several other species of snakes, this individual's measured GGT level could be interpreted to be within normal limits.

An elevated glucose level was found in this animal, and elevated glucose levels can be associated with pancreatitis and diabetes, dietary intake and stress. As the patient's amylase levels were within reasonable levels and there was no history of the patient refusing meals or changes in diet, pancreatitis and dietary causes were low as differentials. It is believed that the elevated glucose was secondary to stress of transport and handling. Total protein, albumen and globulin were all found to be elevated, but in even ratios. If all three of these were mathematically reduced by an equal percentage, all three values would be within normal limits, suggestive of dehydration.

The blood values from the second, post-treatment blood collection indicated a white blood cell count within normal limits with both monocytes and heterophils markedly decreased from the first visit. The monocyte count was still believed to be elevated, but a decrease of over 93% from the original count was strongly suggestive that the primary pathology was resolving. The remaining comparatively

mild elevation was likely due to the small lesions on the caudal aspect of the head and likely chronic immune system stimulation. As the packed cell volume, total protein, and serum sodium levels had all returned to normal or near-normal levels with no change in the albumen: globulin ratio, the previously seen dehydration was believed to be corrected. The mild increase in aspartate aminotransferase (AST) noted in the second sample is believed to be most likely muscle trauma, most likely from the rough handling occurring with the daily treatments given by the owner. Bile acids and GGT levels decreased, indicating improved hepatic condition developing as the septicemia resolved systemically. Glucose was found to have decreased between the first and second sample with only a relatively small change noted in amylase. Although not confirmed, pancreatitis does not appear to be likely as a cause of the initial hyperglycemia, but is rather believed to be secondary to stress of the initial handling, transport and illness. Although still rather fractious, the owner stated that treatment had gotten easier with time and this may be due to the patient acclimatizing to the regular care.

The calcium levels, however, do not offer a direct explanation. The first analysis found them mildly elevated at 19.4 mg/dl (*N. naja* range: 16.9 +/- 1.4 mg/dl) and further elevated at 21.8 mg/dl at the second analysis. Although renal disease, neoplasia and granulomatous disease are all differentials for chronic hypercalcemia, a more likely diagnosis is that this animal, although probed as a potential male, is actually a female and is reproductively active. Endoscopic or DNA sexing would have confirmed this hypothesis.

Although other patients are typically endotracheally intubated following

propofol infusion and/or isoflurane anesthesia, the decision was made not to intubate due to the risk of potential envenomation to the doctor involved and that the procedure would not be invading the coelomic cavity and would be very short (<20 minutes). Had a longer procedure been planned, or had the procedure involved a coeliotomy, the patient would have been intubated and artificially ventilated with available equipment. Furthermore, the patient continued to breathe spontaneously and regularly, but had he not, intubation and ventilation would have been performed.

The owner wanted to see if there was improvement in the condition of the patient with the antibiotics prescribed, but when improvement was not seen within a few days (6 days), the owner understood the importance of the culture. As mentioned, the owner initially declined cultures to be run on both the biopsy and blood samples, and ideally, both of these should have been submitted at the onset to determine the inciting agent(s).

Initial suspected failure of treatment is believed to be due to resistance of the invading pathogenic organisms to cefotaxime. Once results were obtained, the *E. Coli* and *Pseudomonas* was considered the primary concern initially due to pathogenicity of these species of bacteria,^{eee} although they were considered likely secondary infections and/or contaminants. It is recognized that other bacteria may have been present, but as a product of the samples being frozen prior to submission a pathogen may have been eliminated from the culture. Although the *Enterococcus* isolated on culture was initially thought to be an environmental contaminant, the prolonged recovery and delayed healing may have been a result of this potential

pathogen either playing a significant part in the infection at the onset of treatment and/or after the other pathogens had been cleared from the lesions. Had antibiotic therapy that addressed sensitivities of all pathogens identified been prescribed initially, a faster clearing of infection and recovery might have been seen. A better scenario to these types of cases would be that of immediate submission of all samples for culture and sensitivity and then selecting treatment protocols based on sensitivity results, with continual, uninterrupted treatment courses.

Infrequency and inadequacy of care provided is believed to have affected the recovery of the patient. After the first examination and collection of samples, specific aftercare instructions were not followed well. Recovery was seen to not significantly occur until after improved husbandry was provided. The week that passed between the two courses of antibiotics may have facilitated further infection as well as the development of drug resistance. Lack of appropriate temperatures through much of the treatment process delayed appropriate healing processes and inhibited full immune system potential.^w Once recommended thermal care was provided, the healing process went much faster and the snake's skin condition improved.

Slow healing of skin wounds has been well noted in snakes. This was observed in this case, but it was also noted that the fastest healing of the skin lesions occurred at the surgical sites where damaged skin was removed. It is postulated that these sites recovered faster because not only the wounds had been more thoroughly disinfected at the biopsy, but also that the owner may have taken more care to clean the incisional wound sites to prevent infection or dehiscence of the wound.^v In

future cases, it may be advisable to instruct the caretaker to clean all wounds equally well to facilitate healing.

It has been noted in the literature that lesions caused by vesicular dermatitis benefit from covering/bandaging the wounds, and that some wound products inhibit healing.^{fff} Covering the wounds in this case may have helped, but was not feasible in this animal in that the patient was fractious and very active and thus would have rubbed off any physical covering to the skin, and that there was insufficient nursing care for optimal recovery. Had these issues not been a factor, daily bandaging after thorough cleaning and drying would have been prescribed. Liquid “bandage” materials such as “New Skin” or “OpSite Spray” have been used but there has been only mention of the use of these products in squamates. No studies have been done in their use to determine if they have toxic solvents, cytotoxic properties or inhibit/encourage epithelial migration across wounds. Furthermore, there was a concern that these products may allow further bacterial growth by isolating them away from topically-applied cleaners and antiseptics. As a result, these may be products to consider in the future but were not selected in this case due to unknown factors.

This report describes a typical case of vesicular dermatitis in snakes, compounded by the dangerous nature of the species of this patient and the chronicity of the presentation. This condition is common in herptile practice and needs to be managed competently to reach a full recovery. As is most commonly found to be the case, this presentation appeared to have infectious and husbandry origins, and treatment required appropriate antimicrobial and medical therapy as

well as modifications to the housing and care. In the end, a successful outcome was achieved.

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