The Simple Tooth:  
Feline Skull and Tooth Anatomy  
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Skull anatomy
The skull can be divided into the fused bones of the calvarium, the upper jaw, and the lower jaw. The cranial portion of the calvarium consists of the paired frontal bones, which articulate cranially with the nasal bones and maxillae, and caudally with the parietal bones. The nasal cavity contains an ethmoid bone and is bordered dorsally by the incisive, nasal and frontal bones, laterally by the incisive, maxilla, lacrimal, frontal and palatine bones, ventrally by the incisive, maxilla, and palatine bones and caudally by a single vomer bone which lies ventral to the ethmoid and dorsal to the hard palate. The lateral surface of the frontal bone shapes the dorsomedial and caudal aspect of the orbit. The medial and ventral part of the orbit is completed by articulation of the frontal bone with the lacrimal, ethmoid, maxilla, presphenoid and palatine bones. The zygomatic bone forms the lateral boundary of the orbit. The temporal process of the zygomatic bone articulates with the zygomatic process of the temporal bone, forming the zygomatic arch. Caudal to the frontal bones and forming the caudal portion of the cranial vault are the paired parietal bones, which articulate caudally with the occipital bone. Ventrally, the parietal bone joins the temporal and basiphenoid bones.

The upper jaw includes the incisive, maxillary, and palatine bones. The paired incisive bones form approximately one-sixth of the hard palate, and three incisors are rooted in each incisive bone. The incisive bones are bordered dorsally by the nasal bones, caudally by the vomer bone and laterally and caudally by the maxillae. The maxillae extend to the caudal border of the hard palate laterally, but are joined medially by the paired palatine bones to complete the hard palate. The roots of the canine tooth, three premolar teeth, and a single molar tooth are embedded within the alveolar process of each maxilla.

The lower jaw is composed of two mandibles, which are joined rostrally at the cartilaginous symphysis and form a synchondrosis. Each mandible consists of a body and a ramus. The three mandibular incisors, canine tooth, two premolars and single molar are anchored in the dorsal alveolar border of the body of the mandible. The ramus of the mandible contains three processes: the coronoid process, the condylar process, and the angular process. The coronoid process forms the most dorsal part of the mandibular ramus and the angular process is located at the caudoventral aspect of the ramus. The temporomandibular joint is formed by the condylar process of the mandible which articulates in the mandibular fossa of the squamous part of the temporal bone. The condylar process is bar-shaped in the cat, which is typical for carnivores. The mandibular fossa is bordered rostrally by the articular eminence and caudally by the retroarticular process. Both of these bony prominences are well developed in the cat, which creates a very deep mandibular fossa and normally prevents any movement of the mandibular condyle beyond these prominent bony processes.

The temporomandibular joint (TMJ) is a condylar synovial joint, which is separated into a dorsal and ventral compartment by a thin articular disk. The disc attaches around its entire periphery to the joint capsule which creates two separate articular spaces. Normally, when the mouth is opened, the medial aspect of the mandibular condyle is seated firmly in the mandibular fossa. The lateral aspect of the joint capsule is thickened in cats and tenses at maximum jaw opening which functions to limit lateral motion of the condyle. A caudal capsular reinforcement has also been demonstrated in the cat. Construction of the feline TMJ reduces rotary and lateral grinding movements.

Muscles of mastication
The muscles of mastication in the cat include the temporalis, masseter, medial and lateral pterygoids and rostral and caudal digastricus. The masseter, temporalis and pterygoid muscles close the jaw and the digastricus muscle opens the mouth.

Blood supply
The majority of blood supply to the feline oral cavity is provided by the maxillary artery. In the mandible the maxillary artery branches into the mandibular (inferior alveolar) artery which enters the mandibular canal through the mandibular foramen. The mandibular (inferior alveolar) artery courses rostrally within the mandibular canal and then exits laterally through the caudal, middle and rostral mental foramina. Blood supply to the maxilla is provided by the major palatine and infraorbital branches of the maxillary artery. The major palatine artery courses through the caudal nasal cavity, passes though the palatine foramen and courses on the ventral surface of the hard palate midway between midline and the maxillary arcade. The infraorbital artery branches from the maxillary artery and enters the infraorbital canal.

Innervation
Motor innervation to the muscles of mastication is supplied by the mandibular branch of the trigeminal nerve (except the caudal belly of the digastricus which is innervated by the facial nerve). Sensory innervation is received from the maxillary and mandibular...
branches of the trigeminal nerve. The maxillary nerve courses through the pterygopalatine fossa to enter the infraorbital canal. The palatine nerves branch from the maxillary nerve prior at the caudal limit of the infraorbital canal. The caudal maxillary alveolar nerve branches from the maxillary nerve prior to it entering the infraorbital canal. The maxillary nerve becomes the infraorbital nerve when it enters the infraorbital canal. The middle and rostral maxillary alveolar nerves branch from the infraorbital nerve within the canal. The infraorbital nerve exits the infraorbital canal and innervates the lateral and dorsal cutaneous structures of the rostral maxilla and upper lip.

The mandibular branch of the trigeminal nerve enters the mandibular foramen on the lingual side of the mandible, travels in the mandibular canal and exits laterally as the caudal, middle and rostral mental nerves. The middle mental foramen is located in the diastema between the mandibular canine tooth and mandibular third premolar tooth halfway between the dorsal and ventral cortex of the mandible.

Salivary glands

The major salivary glands of the cat are the parotid, zygomatic, mandibular, and sublingual. The parotid salivary duct exits at the papilla which is located in the alveolar mucosa just caudal to the maxillary fourth premolar. The zygomatic salivary duct orifice opens in the alveolar mucosa near the maxillary first molar. The mandibular and sublingual salivary duct orifice opens on a small sublingual papilla located lateral to the rostral end of the tongue frenulum. There are two sets of molar salivary glands in the cat. The lingual molar glands are located linguodistal to the mandibular first molars. The buccal molar salivary glands empty into the oral cavity through several small ducts.

Tooth anatomy

- **Crown** is the portion of the tooth that is covered by enamel which is visible above the gumline.
- **Root** is the portion of the tooth that is covered by cementum located within the alveolus beneath the gingival tissue.
- **Apex** is the area of the root which is the deepest in the alveolar bone.
- **Enamel** is the hardest substance in the body which is the outer layer of the tooth crown. Enamel is formed by ameloblasts within the tooth bud prior to eruption. If enamel is damaged it is incapable of repair.
- **Cementum** is the outer layer of the tooth root which provides a surface for attachment of the periodontal ligament to the tooth.
- **Cementoenamel junction** is the neck of the tooth where the crown meets the root.
- **Periodontal ligament** is the fibrous connective tissue that surrounds the root of the tooth, separating it from and attaching it to the alveolar bone and serving to hold the tooth in place. The periodontal ligament also acts as a shock absorber.
- **Pulp cavity** is the central cavity of the tooth consisting of the pulp chamber and root canal containing blood vessels, nerves, lymph vessels and other cells (odontoblasts). The pulp chamber of the cat lies very close to the enamel surface, so any fracture in a cat’s tooth requires endodontic or exodontic treatment.
- **Dentin** is the living tissue that comprises the bulk of the tooth surrounding the pulp cavity and covered by cementum and enamel. Dentin is 70% inorganic and 30% organic. Dentin is porous containing dentinal tubules which extend from the dentin-cementum or dentin-enamel surfaces of the tooth to the pulp and are responsible for transmission of painful stimuli if the dentin is exposed.
  - **Primary dentin** forms before tooth eruption.
  - **Secondary dentin** is produced by odontoblasts within the pulp after tooth eruption causing the dentin walls to thicken.
  - **Tertiary or reparative dentin** is morphologically irregular dentin that forms in response to an irritant.
• *Alveolar bone* is the thin layer of the mandibular and maxilla that comprises the ‘tooth socket’ and contains teeth.
• *Lamina dura* is a sheet of compact alveolar bone that lies adjacent to the periodontal ligament space. Radiographically it appears as a ‘white line’.

**Gingiva anatomy**
• *Marginal gingiva* is the free gingival tissue that forms the gingival margin surrounding the crown of the tooth.
• *Attached gingiva* is located apical to the marginal gingiva and is tightly adhered to underlying alveolar bone. The attached gingival tissue is coronal to the mucogingival line. The attached gingiva is widest at the maxillary canine teeth in the cat.
• *Mucogingival line* is the junction between the alveolar mucosal tissue and the attached gingival tissue. The mucogingival line remains stationary although the gingival tissues around it may change in size or height (gingival enlargement or gingival recession).
• *Gingival sulcus* is the crevice surrounding the tooth located between the external tooth surface and the marginal gingival tissue. Normal sulcus depth in a cat is less than 1 mm.
• *Junctional epithelium* attaches to the enamel of the most apical portion of the crown. The floor of the gingival sulcus is on the most coronal portion of the junctional epithelial cells.
• *Interdental papilla* is the gingival peak between adjacent teeth.
• *Periodontium* consists of the tissues that surround and support the teeth, including the gingiva, periodontal ligament, cementum and alveolus.

**Types of teeth**
• *Incisors (I)* are small single rooted teeth located in the front of the mouth. They are utilized for cutting, picking up objects and grooming. Cats have six maxillary and six mandibular incisors.
• *Canines (C)* are large single rooted teeth, commonly called ‘fang’ teeth. They are utilized for holding prey, slashing and tearing. The lower canine teeth assist in holding the tongue in place. Cats have a right and left maxillary canine tooth and a right and left mandibular canine tooth.
• *Premolars (PM)* are located on the side of the mouth behind the canines. They are utilized for holding food and for breaking food into smaller pieces. Cats do not have a maxillary first premolar or mandibular first and second premolars. In each maxillary quadrant there is a single rooted second premolar, a two rooted third premolar and a three rooted fourth premolar. In each mandibular quadrant there is a two rooted third and fourth premolar.
• *Molars (M)* are in the back of the mouth and are used for grinding food. Cats have one maxillary first molar and one mandibular first molar.

**Tooth eruption times**

<table>
<thead>
<tr>
<th>Deciduous teeth (weeks)</th>
<th>Permanent teeth (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incisor</td>
<td>2-3</td>
</tr>
<tr>
<td>Canine</td>
<td>3-4</td>
</tr>
<tr>
<td>Premolars</td>
<td>3-6</td>
</tr>
<tr>
<td>Molars</td>
<td></td>
</tr>
</tbody>
</table>

Remember there are no deciduous precursors for the molar teeth in a cat. The maxillary teeth usually erupt prior to their mandibular counterparts. The incisors generally erupt first, followed by the canine teeth then premolars and molars.

**Feline dental formulas**

<table>
<thead>
<tr>
<th>Deciduous</th>
<th>Permanent</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 1 3</td>
<td>3 1 3 1</td>
</tr>
<tr>
<td>3 1 2</td>
<td>3 1 2 1</td>
</tr>
</tbody>
</table>

| total teeth = 26 | total teeth = 30 |

**Permanent tooth development**

At the time of permanent tooth eruption, the apex is incomplete and there is a very wide pulp cavity with primary dentin present. As the tooth continues to develop the apex closes and secondary dentin is produces by odontoblasts within the pulp cavity. As the cat continues to mature the pulp cavity continues to get smaller as the secondary dentin layer increases in thickness.
Directional nomenclature

- Mesial – toward the midline of the dental arch
- Distal – farthest away from the midline of the dental arch
- Vestibular – next to or toward the lips; buccal and labial are also acceptable
- Labial – next to or toward the lips
- Buccal – toward the cheek
- Lingual – next to or toward the tongue
- Palatal – toward the palate
- Apical – toward the apex (root)
- Coronal – toward the crown
- Rostral – anatomical term applicable to the head referring to a structure closer to the most forward structure of the head
- Caudal – anatomical term applicable to the head referring to a structure closer to the tail

Occlusion

Class 0 normal occlusion

- Scissors bite with the maxillary incisors overlapping, but touching the mandibular incisors in a scissor-type fashion. The maxillary incisors should be slightly rostral to the mandibular incisors. A level bite is also acceptable in cats.
- The mandibular canine teeth interdigitate in the interproximal space equidistant between the maxillary lateral incisor and canine tooth.
- The maxillary premolars interdigitate with the mandibular premolars in a “pinking shears” fashion.
- Cusp of the maxillary fourth premolar should be buccal to the mandibular first molar.

Class 1 malocclusion

- Neutrocclusion, normal jaw lengths
- Individual teeth are malaligned
- Lingually displaced mandibular canine tooth, mesioversion maxillary canine tooth, rostral crossbite, caudal crossbite

Class 2 malocclusion (mandibular distocclusion)

- Mandible is shorter than the maxilla (mandibular brachygnathism)’overbite’ ‘parrot mouth’

Class 3 malocclusion (mandibular mesiocclusion)

- Maxilla is shorter than the mandible (mandibular prognathism)’underbite’

Class 4 asymmetrical malocclusion

- Can occur in a rostro-caudal, side-to-side, or dorso-ventral direction

Triadan tooth identification system

The modified Triadan system (3 numbers for each tooth) is considered to be the tooth numbering system of choice in veterinary dentistry.

The first number indicates the quadrant that the tooth is in and whether the tooth is a permanent or deciduous tooth

- Permanent tooth first numbers
  - 1 – Right maxilla
  - 2 – Left maxilla
  - 3 – Left mandible
  - 4 – Right mandible

- Deciduous tooth first numbers
  - 5 – Right maxilla
  - 6 – Left maxilla
  - 7 – Left mandible
  - 8 – Right mandible

The second and third digits indicate the tooth position within the quadrant with the sequence starting at the midline. So, 01 is the first tooth on the midline (the first incisor) and the numbering continues sequentially away from the midline.

- Rule of 4, 8 and 9
  - 04 is always the canine tooth
  - 08 is always the fourth premolar
  - 09 is always the first molar

Rules to remember

Remember there is not a maxillary right or left first premolar in the cat (105, 205) and there is not a mandibular right or left first or second premolar in the cat (405, 406, 305, 306).
Knowledge of normal anatomy of the cat skull and oral cavity allows the veterinarian to properly evaluate and treat oral and maxillofacial diseases.
Oral Surgery to Extract Teeth in Cats: Tips and Techniques to Avoid Complications

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The goal of all extractions is to extract the entire tooth and root without damage to surrounding structures. One of the most common complications of tooth extraction is fracture of the tooth root. In addition, tooth extraction can result in: displacement of the root tip into the mandibular canal, nasal cavity or maxillary sinus; hemorrhage; mandibular and maxillary fractures; oronasal fistulas; and ophthalmic complications.

The easiest way to avoid surgical complications is through adequate preparation. Preoperative radiographs should always be obtained prior to starting oral surgery to carefully evaluate the entire tooth, including the apex and the surrounding bone. Proper instrumentation, including a high speed handpiece and sharp dental elevators, will assist in successful extraction. It is important that the operator use controlled forces and proper technique when extracting teeth. In addition, the skill and knowledge of the veterinarian should always be considered. If you are not comfortable with a particular procedure based on your knowledge, skill and/or the pathology that is present, it is best to refer the patient to a board certified veterinary dentist.

Inadequate crown removal during coronectomy
Sometimes when completing coronectomy for a tooth that is very close to the adjacent tooth, a portion of the tooth crown is inadvertently left on the mesial or distal side of the tooth. When left behind, this small crown remnant is painful and usually results in a focal area of inflamed gingival tissue. Always obtain post coronectomy radiographs to ensure adequate crown removal.

Fractured tooth roots
It is important to remove adequate alveolar bone and section all multi-rooted teeth prior to attempting elevation of the tooth roots. Often the bad sound of a cracking root will give the operator a clue to the potential for an existing complication. Always inspect the extracted tooth root for a smooth round apex. If there is a rough or jagged edge to the root, chances are there is still a root remnant remaining in the alveolus. Always take post extraction radiographs to document the extraction of the entire tooth and root without damage to the surrounding bone. Sometimes, despite our best attempts, tooth roots fracture during oral surgery to extract the tooth.

The following steps will allow for easier retrieval of fractured tooth roots:

1. Keep the fractured tooth to ‘recreate the scene of the crime’. The fractured root end will usually be sharp and irregular. If the fracture is oblique, visualization of this angle allows us to determine how the remaining tooth root is positioned within the alveolus. Starting with the portion of the retained root that is most coronal (circle), allows insertion of the dental elevator into the periodontal ligament space in that location for easier removal of the remaining root tip.

2. Radiograph the remaining root tip to evaluate how much root structure remains and how the remaining root structure appears. Note what structures the root apex is adjacent to, if there is any pathology associated with the surrounding bone, and if there is an abnormal shape to the remaining root segment.

3. Elevate the remaining root fragment. If the fractured root tip is visible and it is possible to position the dental elevator or root tip pick into the periodontal ligament space, the first option is to elevate the remaining root segment without removal of additional bone. Carefully rotate the elevator to elevate and extract the remaining root tip. Do not place apical pressure on the root tip to avoid displacement of the root tip into the mandibular canal, nasal cavity or maxillary sinus. Be sure you can clearly visualize the periodontal ligament space and the root! If you cannot, remove additional buccal alveolar bone.

4. Remove additional buccal alveolar bone to outline the remaining root tip and periodontal ligament space on the mesial and distal root surfaces. Often the fracture occurs at the level of the initial alveolar bone removal. How much buccal alveolar bone can you remove? As much as necessary to safely remove the fractured tooth root without damaging the surrounding bone and soft tissues. Be careful with excessive bone removal in the mandibles of small dogs and cats. Be aware of the anatomy in the area, especially taking into consideration the neurovascular bundles.

In the illustration below, the initial buccal bone has been removed to the level where the root fractured (black horizontal line). Careful removal of additional buccal alveolar bone, as illustrated with the red shaded area, allows for exposure of more of the retained root tip and assists in identification of the periodontal ligament space.
1. Utilize small dental elevators in the periodontal ligament space with rotating pressure, *no apical pressure*, to carefully elevate and extract the remaining root fragment. Excessive apical pressure can displace the root segment into the nasal cavity, maxillary sinus or mandibular canal.

2. In the case of small fractured root tips a 20, 22 or 18 gauge needle can be utilized as an elevator by placing it in the periodontal ligament space and gently rotating the needle (do not apply apical pressure). The needle may also be utilized to gently ‘lever’ the root tip into the open alveolus.

3. Another aid to assist in the extraction of root tips is to introduce a small round bur (#1 or #1/2) into the alveolus to create a ‘moat’ around the root to allow introduction of an instrument (elevator or root tip pick) into this space for root tip elevation and removal.

4. Utilize root tip extraction forceps with gentle rotation to assist in removing fractured roots. Root tip extraction forceps are utilized only once the root tip is mobile.

What if the attempt to remove the root tip is unsuccessful? When can root tips be left in place? Root tips can be left in place only if the risks of surgery to remove the root tip outweigh the benefits of removing the root tip. A root tip may not be left in place if there is any evidence of periodontal disease or endodontic disease (periapical lysis) associated with the root tip. To leave a fractured root tip in place, the root tip must be small, deep within the alveolus and must not be infected or have periapical lysis. The risks of surgery that may outweigh the benefits of the root tip removal may include: the patient is not stable under anesthesia; continued attempts at root retrieval may impact vital structures (nerves and vessels within the mandibular canal, the nasal cavity or orbit); or continued attempts may result in significant destruction of surrounding bone or soft tissues. If the decision is that the benefit of fractured root removal does not outweigh the risks, and the root tip will remain in place, then an intraoral radiograph must be taken to document the remaining root structure. The owners must be informed of the decision, the reason for the decision and the possible clinical sequelae that may result from the decision. Radiographs of the retained root should be obtained annually to determine if there is any pathology associated with the remaining root fragment.

Fractured root tips are frustrating and sometimes difficult to remove. Proper extraction technique will minimize the chances for fracturing root tips. Intraoral radiographs prior to extraction are necessary to evaluate the tooth structure and surrounding alveolar bone. Removal of buccal alveolar bone and proper sectioning of teeth facilitates extraction. The use of proper, sharp instruments and slow controlled forces is recommended. Above all, be patient.

**Displacement of root tips into mandibular canal, nasal cavity or maxillary sinus**

While attempting to retrieve fractured root tips it is possible to displace a tooth root into the mandibular canal, nasal cavity or maxillary sinus. Careful elevation of fractured root tips with minimal apical force will assist the operator in preventing root tip displacement. After displacement, it is desirable to remove the root tip or tooth fragment. Removal is usually facilitated by removal of additional bone and careful evaluation to identify the displaced root tip. If this procedure is beyond the capability of the operator the case should be referred to a veterinary dental specialist.

**Hemorrhage and trauma to soft tissues**

Excessive bleeding may originate from the extraction site or from trauma to vascular structures or soft tissue during the extraction. Hemorrhage usually results from the use of uncontrolled forces with the dental elevator and ‘slipping’ into the sublingual area, buccal mucosal tissue, infraorbital vessels or mandibular canal. Bleeding may occur after the tooth root is extracted if there is a large area of granulation tissue present at the tooth apex. Hemorrhage can usually be controlled with ligation of the lacerated vessel, direct pressure, utilization of an absorbable hemostatic gelatin sponge, or suturing of the gingiva over the alveolar to allow formation of a clot.
Mandibular and maxillary fractures
Pathologic or iatrogenic mandibular fractures occur most commonly secondary to extraction of the mandibular canine tooth in the cat. The fracture may occur due to preexisting periodontal disease or excessive force used by the operator or a combination of both. Pre-extraction radiographs are always indicated as they allow for an accurate assessment of the surrounding alveolar bone and are necessary to assist the operator in planning for a successful surgical extraction. Creation of a mucogingival flap, removal of buccal bone, followed by very careful elevation and extraction of the affected tooth with controlled forces will assist in prevention of mandibular fractures secondary to tooth extraction.

Oronasal fistula
The shelf of bone separating the oral cavity from the nasal cavity is very thin on the palatal side of the maxillary canine tooth. Periodontal disease leads to vertical bone loss and the resulting oronasal fistula. An oronasal fistula may also occur if the maxillary first, second and third premolars are affected by severe periodontal disease. If an oronasal fistula is visible at the time of extraction, debridement and primary closure with a mucogingival flap is indicated. Chronic oronasal fistulas can lead to mucopurulent or hemorrhagic nasal discharge and/or sneezing.

Ophthalmic complications
The apices of the maxillary fourth premolar and first molar in the cat lie in close proximity to the ventral floor of the orbit. There is a thin shelf of alveolar bone surrounding these tooth roots. The orbit can be penetrated with a dental elevator if the tooth is affected by periodontitis and if a short finger stop is not utilized during extraction. Penetration of the globe may result in panophthalmitis or may ultimately result in enucleation of the affected eye. Use of controlled forces and a finger stop will assist the operator in prevention of this complication.

Neoplasia
Continued gingival inflammation in the area of previously extracted teeth or a non-healing oral surgery site in cats is may be due to underlying neoplasia. Pre-extraction radiographs allow for the evaluation of the alveolar bone surrounding the mobile teeth prior to extraction. Depending on the radiographic findings, the operator may elect to biopsy the soft tissue and bone rather than extract mobile teeth. Mobile teeth ALWAYS require intraoral radiograph prior to extraction.

The goal of all extractions is to extract the *entire* tooth and root without damage to surrounding structures. Unfortunately, we all will encounter complications during tooth extraction at some point in our career. Recognition of the potential complications and knowledge of appropriate treatment methods for those complications will assist in minimizing pain and discomfort for our patients. The easiest way to avoid surgical complications is through adequate preparation and evaluation of the tooth and surrounding bone structure and utilization of proper instrumentation with controlled forces during tooth extraction.
The goal of all extractions is to extract the entire tooth and root without damage to surrounding structures. One of the most common complications of tooth extraction is fracture of the tooth root. In addition, tooth extraction can result in: displacement of the root tip into the mandibular canal, nasal cavity or maxillary sinus; hemorrhage; mandibular and maxillary fractures; oronasal fistulas; and ophthalmic complications.

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1.保持骨折的牙齿以‘重现犯罪现场’。骨折的根部通常会锋利不规则。如果骨折是钝的，视觉化这个角度能帮助我们确定剩余牙根是否位于牙槽内。
2. 用牙根尖端的牙周袋空间进行插入。如果可以，可以使用牙周袋空间将剩余牙根片状提取。
3. 用牙周袋空间产生对剩余牙根片状的额外骨组织。
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While attempting to retrieve fractured root tips it is possible to displace a tooth root into the mandibular canal, nasal cavity or maxillary sinus. Careful elevation of fractured root tips with minimal apical force will assist the operator in preventing root tip displacement. After displacement, it is desirable to remove the root tip or tooth fragment. Removal is usually facilitated by removal of additional bone and careful evaluation to identify the displaced root tip. If this procedure is beyond the capability of the operator the case should be referred to a veterinary dental specialist.

**Hemorrhage and trauma to soft tissues**

Excessive bleeding may originate from the extraction site or from trauma to vascular structures or soft tissue during the extraction. Hemorrhage usually results from the use of uncontrolled forces with the dental elevator and ‘slipping’ into the sublingual area, buccal mucosal tissue, infraorbital vessels or mandibular canal. Bleeding may occur after the tooth root is extracted if there is a large area of granulation tissue present at the tooth apex. Hemorrhage can usually be controlled with ligation of the lacerated vessel, direct pressure, utilization of an absorbable hemostatic gelatin sponge, or suturing of the gingiva over the alveolar to allow formation of a clot.
**Mandibular and maxillary fractures**
Pathologic or iatrogenic mandibular fractures occur most commonly secondary to extraction of the mandibular canine tooth in the cat. The fracture may occur due to preexisting periodontal disease or excessive force used by the operator or a combination of both. Pre-extraction radiographs are always indicated as they allow for an accurate assessment of the surrounding alveolar bone and are necessary to assist the operator in planning for a successful surgical extraction. Creation of a mucogingival flap, removal of buccal bone, followed by very careful elevation and extraction of the affected tooth with controlled forces will assist in prevention of mandibular fractures secondary to tooth extraction.

**Oronasal fistula**
The shelf of bone separating the oral cavity from the nasal cavity is very thin on the palatal side of the maxillary canine tooth. Periodontal disease leads to vertical bone loss and the resulting oronasal fistula. An oronasal fistula may also occur if the maxillary first, second and third premolars are affected by severe periodontal disease. If an oronasal fistula is visible at the time of extraction, debridement and primary closure with a mucogingival flap is indicated. Chronic oronasal fistulas can lead to mucopurulent or hemorrhagic nasal discharge and/or sneezing.

**Ophthalmic complications**
The apices of the maxillary fourth premolar and first molar in the cat lie in close proximity to the ventral floor of the orbit. There is a thin shelf of alveolar bone surrounding these tooth roots. The orbit can be penetrated with a dental elevator if the tooth is affected by periodontitis and if a short finger stop is not utilized during extraction. Penetration of the globe may result in panophthalmitis or may ultimately result in enucleation of the affected eye. Use of controlled forces and a finger stop will assist the operator in prevention of this complication.

**Neoplasia**
Continued gingival inflammation in the area of previously extracted teeth or a non-healing oral surgery site in cats is may be due to underlying neoplasia. Pre-extraction radiographs allow for the evaluation of the alveolar bone surrounding the mobile teeth prior to extraction. Depending on the radiographic findings, the operator may elect to biopsy the soft tissue and bone rather than extract mobile teeth. Mobile teeth ALWAYS require intraoral radiograph prior to extraction.

The goal of all extractions is to extract the *entire* tooth and root without damage to surrounding structures. Unfortunately, we all will encounter complications during tooth extraction at some point in our career. Recognition of the potential complications and knowledge of appropriate treatment methods for those complications will assist in minimizing pain and discomfort for our patients. The easiest way to avoid surgical complications is through adequate preparation and evaluation of the tooth and surrounding bone structure and utilization of proper instrumentation with controlled forces during tooth extraction.
Shades of Gray: Interpretation of Feline Dental Radiographs
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As with any new piece of equipment in veterinary hospitals, there is a learning curve associated with dental radiography – both in obtaining diagnostic dental radiographs and interpretation of dental pathology.

With digital images, the image appears on the computer screen. When obtaining intraoral radiographs the following tips will help you orient the image in the same way each time for evaluation. Some veterinary software programs will label the images with the tooth number or tooth as you expose them. First, if the tooth being imaged is a maxillary tooth the tooth crowns should point down and if the tooth being imaged is a mandibular tooth the tooth crowns should point up. Remember that all three rooted teeth are located in the maxilla. The presence of the palatine fissures, nasal passages and sinuses indicate the tooth is in the maxilla. Visualization of the mandibular canal or ventral cortex of the mandible confirms that the tooth is a mandibular tooth. After determining if the tooth is in the maxilla or mandible then determine if you are viewing the right or left side. When viewing the right side of the mouth the anterior teeth are on the right side of the image and when viewing the left side of the mouth the anterior teeth are on the left side of the image. Depending on the imaging software the images may appear on the computer screen in the correct orientation.

When mounting full mouth radiographs, the patient’s right maxilla and right mandible are on the viewer’s left side and the patient’s left maxilla and left mandible are on the viewer’s right side. (Remember that the viewer is standing on the outside of the patient’s mouth looking at the patient.)

Knowledge of normal anatomy of the tooth, mandible and maxilla is essential for the proper evaluation of dental radiographs. The components of the tooth and its supporting structures are usually well defined on dental radiographs. These structures include the following:

- **Enamel:** the outermost layer of the crown of the tooth
- **Cementum:** the outermost layer of the root of the tooth
- **Cementoenamel junction:** area where the cementum and enamel meet
- **Dentin:** radiopaque layer between the outermost surfaces of the crown and root and the radiodense pulp cavity
- **Pulp cavity:** radiodense area within the tooth and roots including the pulp chamber, pulp horns and root canal.
- **Periodontal ligament space:** thin radiolucent area between the root of the tooth and the lamina dura
- **Lamina dura:** the cribiform plate and dense alveolar bone surrounding the root which appears as a radioopaque line adjacent to the periodontal ligament space
- **Alveolar bone:** encases and supports the tooth structure
- **Alveolar margin:** most coronal portion of the alveolar bone, located between teeth, composed of dense cortical bone
- **Furcation:** the anatomic area of a multi-rooted tooth where the roots diverge
• **Periapical:** the area around the tooth apex

The mandibular canal is visible as a radioluency of uniform width in the mandible parallel to the ventral border of the mandible. The caudal, middle and rostral mental foramen may be mistaken for periapical pathology in the area of the mandibular premolars. The middle mental foramen is located distal to the apex of the canine tooth in the cat. (To distinguish the foramen versus a periapical lucency, change the horizontal angle of the tubehead. If the lucency remains associated with the apex of the tooth it is indeed a periapical lucency. The foramen will move relative to the root as the horizontal angle of the tubehead is changed.) The mandibular symphysis appears as a linear radiolucent line between the central incisors.

In the maxilla the symmetrical radiolucent structures which appear distal to the maxillary incisors are the palatine fissures. The junction of the vertical body of the maxilla and its palatine process is visualized as a radiopaque line that crosses the midroot section of the maxillary canine tooth.

Radiographs should include the entire crown and root of the tooth being imaged and 3 mm of alveolar bone around the tooth apex. The following generalizations can be made about dental radiograph interpretation.

Radiographic signs of feline tooth resorption include defects present at the cementoenamel junction and/or roots with evidence of root replacement. Clinically, there are two types of tooth resorption in cats. Tooth resorption type I lesions have normal root density and a well-defined periodontal ligament space around the root tooth. Often these teeth have associated horizontal or vertical bone loss. Tooth resorption type II lesions have root replacement resorption with no discernible periodontal ligament space and the roots appear to blend in with the surrounding bone. Both types of tooth resorption can be found in the same cat and even in the same tooth. Differentiation between type I and type II tooth resorption in feline patients is important to determine the appropriate treatment for these teeth. Type I tooth resorption is treated by extraction of the entire tooth and root. Type II tooth resorption is treated by crown amputation with intentional root retention.

Radiographic signs of periodontal disease may include: widening of the periodontal space; resorption of the alveolar crest; decreased alveolar bone density and horizontal, vertical, angular or furcation bone loss. Remember that 30-60% of the bone must be lost before it is visible radiographically. Horizontal bone loss involves the buccal, lingual and interdental portions of bone and appears as decreased alveolar marginal bone around the tooth. Vertical bone loss usually appears as an area of decreased bone density surrounding the tooth root and may appear to as a ‘V’ shape adjacent to the tooth root. It is important to recognize that clinical examination in combination with dental radiographs is necessary to properly diagnose periodontal disease. Mild bone loss, stage 1 furcation exposure, vertical bone loss on the palatal side of the maxillary canine teeth may not be visible radiographically, only clinically. In addition, proper exposure is necessary to evaluate the alveolar bone margin. Overexposure of the dental radiograph may result in ‘burnout’ of the alveolar bone margin and interdental bone.

Radiographic signs of endodontic disease include changes associated with the bone surrounding the tip of the root (periradicular area) and changes within the pulp cavity or tooth itself. Radiographs to evaluate a tooth for endodontic disease should include: the entire root tip and the surrounding bone. The characteristic radiographic lesion of endodontic origin (LEO) involves changes in the periapical radiopacity (often appearing as a radiolucency) or detail that results from apical periodontitis. Lesions of endodontic origin can also develop along the lateral aspect of the root at the site of a lateral canal. Remember that lack of radiographic lesions does not rule out endodontic disease.

Radiographic signs of endodontic disease that are associated with the tissues around the tooth may include: increased width of the periodontal ligament space, loss of the radiopaque lamina dura, diffuse periapical lucency, well defined periapical lucency, or a diffuse area of radiopacity.

Radiographic changes within the tooth are often associated with endodontic disease. When a permanent tooth first erupts, the apex is open, the pulp canal is very wide and the primary dentin layer is thin. Next, the apex closes and then as the tooth continues to mature, the odontoblasts within the pulp canal continue to lay down dentin (secondary dentin). As the tooth continues to mature, the secondary dentin becomes thicker as the pulp canal decreases in width. Radiographically, a tooth that became non-vital during the maturation process will have a pulp canal larger than the contralateral tooth indicating arrested tooth maturation. A seemingly narrow pulp cavity can result from pulpitis that is generalized over a section of the root canal.

Internal root or crown resorption, caused by inflammation in the pulp, appears as an irregularly shaped root canal system. Internal root resorption results from removal of dentin from the wall of the pulp cavity. An internal resorption lesion does not move with change in horizontal angle of the beam of the radiograph (it stays associated with the root canal system).

External resorption resulting from inflammation in the periodontal ligament appears as an irregular defect in the external surface of the tooth root. An external root resorption that is overlying the root canal system will move relative to the root canal system with a change in horizontal angulation of the beam of the radiograph.

• Radiographic signs of aggressive jaw lesions include:
  - Lytic areas of variable size or uniformly pinpointed
  - Indistinct margins
- Lysis of the cortex
- Layers of varied opacity or sunburst effect
- Teeth in position, floating in space
- Bone is moth eaten in appearance
- Root structure is irregular
- Increased tooth mobility

- Radiographic signs of non-aggressive jaw lesions include:
  - Well defined areas of lysis
  - Distinct regular, smooth or sclerotic margins
  - Expanding or thinning of cortex
  - Uniform opacity or lamellar onion skin pattern
  - Displaced teeth
  - Tooth mobility may be affected

Dental radiography is an essential part of the evaluation of oral and maxillofacial diseases. In combination with a complete extraoral and intraoral examination, including the use of a dental probe and explorer, intraoral radiography makes dentistry a science based on fact and provides veterinarians with the tools to properly evaluate and treat oral disease.
Feline Oral Tumors: Diagnosis and Treatment
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Oral tumors account for 7-12% of all feline tumors and 90% of oral tumors in cats are malignant. They may be of dental (odontogenic) or non-dental origin. Squamous cell carcinoma is the most common oropharyngeal cancer in cats accounting for 60-80% of all oral tumors, followed by fibrosarcoma which accounts 13-22% of feline oral tumors.

History and clinical signs
Cats with oral tumors may present with drooling, exophthalmos, facial swelling, epistaxis, sneezing, weight loss, dysphagia, anorexia, decreased appetite, reluctance to eat hard food, decreased activity, hiding and less interactive, halitosis, an unkempt haircoat due to poor grooming, and/or pain when opening the mouth. Beware that loose teeth in a cat with otherwise good dentition could indicate an underlying neoplastic process causing bone lysis.

Clinical staging
Clinical staging of the tumor should be completed utilizing the TMN system which involves assessment of the primary tumor (T), assessment for metastasis to distant sites (M) and to regional lymph nodes (N).

Evaluation of the primary tumor (T)
Evaluation of the primary tumor should include a clinical examination, diagnostic imaging and histopathological evaluation. The size and location of the tumor, the presence of any ulceration or necrosis, and any abnormal mobility of associated teeth should be noted. Clinical features suggestive of a malignancy include rapid growth, fixation to underlying tissue, displacement of teeth, facial deformity, ulceration, and poorly defined margins. Clinical features suggestive of a benign oral mass include an expansile, fluid filled mass.

Diagnostic imaging of the tumor
Dental radiographs should be obtained of the affected jaw to evaluate the extent of involvement of adjacent teeth and alveolar bone associated with the mass. Bone lysis is not radiographically apparent until more than 40% of the cortex of the bone is demineralized. Therefore, radiographs usually underestimate the extent of the tumor. Computed tomography is a valuable and more sensitive diagnostic tool for evaluation of bone invasion and possible extension of the oral tumor into the nasal cavity, caudal pharynx and orbit. CT imaging should be utilized for maxillary tumors and caudal mandibular tumors.

Incisional biopsy
An incisional biopsy is the procedure of choice for most oral soft tissue tumors. Punch biopsy has been shown to produce fewer artifacts than scalpel biopsy. Biopsies should be at least 4-6 mm in diameter with a depth of at least 2 mm. For incision of a hard tissue mass, consider the use of a Michel trephine. It is important to obtain the biopsy from within the oral cavity and not through the lip to avoid seeding the tumor cells into normal skin. Keep in mind the planned definitive surgical resection when obtaining biopsies. The biopsy should always be obtained within the the worst part of the lesion. Multiple biopsies may be obtained. Avoid necrotic and infected areas of the tumor and do not sample at the margin of the mass. When obtaining the biopsy consideration should be given to the plan for definitive surgery so the biopsy site is included in the definitive surgery.

Evaluation for distant metastasis (M)
Three view thoracic radiographs or thoracic CT should be evaluated for distant metastasis. CT is significantly more sensitive than thoracic radiographs for detecting soft tissue nodules. The lower size threshold is 1 mm to detect pulmonary nodules on CT images and 7-9 mm to reliably detect pulmonary nodules on radiographs. Cats less frequently develop the classical well defined appearance of lung metastasis. Metastatic disease can appear as ill-defined mass lesions or diffuse alveolar, interstitial or mixed patterns.

Lymph node evaluation (N)
Lymph nodes may be assessed by palpation to evaluate size, mobility, firmness, single vs multiple nodes, ipsilateral vs contralateral and bilateral distribution. Lymph node size is not a reliable predictor of metastasis. Remember that the lymph nodes that drain the oral cavity in the cat include the mandibular, parotid and medial retropharyngeal. Ruling out mandibular lymph node metastasis does not rule out metastatic disease. Lymph node evaluation may include fine needle aspirate of mandibular lymph nodes and/or evaluation of the other lymph nodes during CT evaluation of the oral mass.
Squamous cell carcinoma (SCC)
Squamous cell carcinoma is the most common oral tumor in cats accounting for approximately 65% of all oral tumors. Affected cats tend to be older, but may be as young as 5 months to as old as 21 years of age with a median age of 12 years. There is no gender predilection. Various studies have shown an increased incidence of squamous cell carcinoma in cats that wear flea collars, cats that are exposed to environmental smoke, and cats with high canned food intake.

Squamous cell carcinoma in cats most often affects the frenulum and ventral surfaces of the tongue. The gingival tissue adjacent to the maxilla and mandible is second most common site. It is uncommon for the tonsil in the cat to be the primary location for a squamous cell carcinoma. Most squamous cell carcinomas occur caudal to the canine teeth. Squamous cell carcinoma is very invasive into the gingival tissue and underlying bone and may extend to involve the palate, pharynx or ramus of the mandible.

Bone invasion in feline squamous cell carcinoma is usually extensive and radiographically these cancers cause an intensely sclerotic, periosteal proliferation in the mandible. Marked osteolysis can also occur. In a study of cats with mandibular swellings only 50% had a tumor and osteomyelitis could not be differentiated from cancer based on radiographic appearance.

Nodal metastasis is seen in about 10% of affected cats. When lymph node metastasis is present the mandibular and retropharyngeal lymph nodes are most commonly affected. Lung metastasis in cats is rare, though it is not possible to determine a true metastatic rate since so few cats have their local disease controlled.

Squamous cell carcinoma in cats is very frustrating to treat as most cases are diagnosed at a late stage in the disease process, leading to few viable treatment options. There is no known effective treatment that consistently yields disease control or survival. If the tumor is located in the rostral mandible and discovered early in the course of disease a mandibulectomy and/or radiation treatment might be considered. Radiation therapy in conjunction with surgery or used alone still results in local recurrence of the tumor. Chemotherapy alone or in combination with radiation therapy has done little to improve survival times in cats with squamous cell carcinoma. The best treatment for squamous cell carcinoma has yet to be determined. Unfortunately palliative care is the most common method of treatment due to poor prognosis and extensive tumor involvement at the time of diagnosis. Palliative treatment may include tube feeding, analgesics and anti-inflammatory drugs. Overall median survival time in cats with squamous cell carcinoma is 44 days. Cats with squamous cell carcinoma have a poor prognosis with a one year survival of less than 10%.

Fibrosarcoma
Oral fibrosarcoma is the second most common oral tumor in cats and does not have a site predilection. Age of affected cats ranges from 1 to 21 years with a mean of 10.3 years. These tumors are locally invasive and metastasis is rare. The tumor arises from the submucosal stroma and is accompanied by local tissue destruction and invasion of skeletal muscle and bone. The preferred treatment is surgical excision with wide margins. As with squamous cell carcinomas, surgical excision is usually not possible due to the advanced disease at the time of diagnosis. Palliative radiation can be considered.

Osteosarcoma
Feline osteosarcoma accounts for 2.4% of all oral tumors and occurs most commonly in older cats with a median age of 10.5 years. Mandibulectomy alone or in combination with radiation or chemotherapy was associated with a 1-3 year survival rate and progression free rate of 83%.

Treatment of fibrosarcoma and osteosarcoma with mandibulectomy showed more than 80% of cats with osteosarcoma and 66% of cats with oral fibrosarcoma were alive three years after surgery. Radiation was used in some of these cases with incomplete surgical margins. Remember to support cats with feeding tubes after mandibulectomy.

Melanoma
Oral melanoma is rare in cats (less than 3% of oral tumors). Metastatic disease is common in cats with oral melanoma. In a small study, median survival of cats with oral melanoma was less than 5 months and no cat lived longer than 8 months.

Lymphoma
Oral and tonsillar lymphoma has been reported in cats, with 11 (2.9%) of a total of 371 cats affected. The appearance was described as single or multiple raised submucosal masses composed of unencapsulated sheets of neoplastic lymphoid cells. Radiation treatment alone or in combination with chemotherapy has been used to treat cats with oral lymphoma.

Salivary gland tumors
Salivary adenocarcinomas originate from the major (parotid, mandibular, sublingual, zygomatic) or minor salivary glands. Minor salivary glands include the lingual molar salivary gland and other salivary glands that can be found in the lip, cheek palate, gingival, tongue and floor of the mouth. Salivary adenocarcinomas can be very invasive. Up to 80% of cats have lymph node metastasis at the time of diagnosis. Pulmonary metastasis is less common. Surgical excision is the treatment of choice. The tumors are often very
invasive extending into surrounding skin and musculature. With surgical excision, regrowth and lymph node metastasis are common. Combination treatment with surgical excision, radiation treatment and chemotherapy is recommended.

**Osteoma**
Osteoma is an uncommon benign bone tumor in cats composed of mature compact or cancellous bone that generally grows continuously and at a slow rate. Osteomas occasional occur in the oral and maxillofacial region. Treatment is recommended early in the course of the disease and involves debulking and recontouring of the affected area. When diagnosed at an advanced state of disease a more aggressive surgical resection may be required. There is debate regarding the etiology and pathogenesis of the osteoma. Some suggest that it is a true neoplasm whereas others classify it as a developmental anomaly triggered by infection or trauma and exacerbated by muscle traction.

**Odontogenic tumors**
Odontogenic tumors originate from the remnants of the embryonic tissues destined to develop into teeth and associated structures and account for 2.5% of all feline tumors. They are classified as inductive tumors when they retain the ability to induce reactive proliferation of connective tissue. Inductive odontogenic tumors include feline inductive odontogenic tumor (FIOT), dentinoma and ameloblastic, complex and compound odontomas. Non inductive tumors in cats include ameloblastomas and calcifying epithelial odontogenic tumors (CEOT).

**Odontoma**
An odontoma is an odontogenic tumor containing epithelial and mesenchymal cells which results in formation of all dental tissue types. The tumor is benign and slow growing but they can be expansile and can create a mass like effect in the oral tissues. Clinically an odontoma will appear as an unerupted tooth or a partially erupted tooth with an associated swelling. A compound odontoma contains rudimentary tooth like structures. An odontoma in which the conglomerate of dental tissues bears no resemblance to a tooth is called a complex odontoma. Treatment for an odontoma is removal of the mass and associated tooth like particles and curettage of the defect.

**Dentigerous cyst**
A dentigerous cyst is a benign, non neoplastic, well circumscribed, cystic lesion associated with an impacted tooth. The fluid filled cyst forms around the tooth crown and is attached to the neck of the unerupted tooth. The resulting lesion is an expansile lesion and can cause a significant bone loss and destruction. Dental radiographs show a unilocular radiolucent area associated with the crown of the unerupted tooth. During normal adult tooth development the inner and outer enamel epithelium are responsible for the production of enamel. After the enamel is formed these tissues fuse to become the reduced enamel epithelium which is a tight sac around the enamel. As the tooth erupts this tissue becomes the junctional epithelium. When tooth does not erupt normally, the ameloblasts persist and form a sac lined with epithelium which may lead to formation of a dentigerous cyst. Treatment for a dentigerous cyst is surgical removal of the tooth and associated cyst lining.

**Feline inductive odontogenic tumor (FIOT)**
Feline inductive fibroameloblastomas is a raised submucosal soft tissue mass typically located in the rostral maxilla in young cats 8-18 months of age. The tumor is locally invasive and metastasis has not been reported. Intraoral radiographs show bone lysis, production and expansion of the maxillary and mandibular bones. and areas of mineralization within the tumor. Wide surgical excision is the treatment of choice and complete excision is considered curative.

**Amyloid producing odontogenic tumors (APOT)**
Although previously referred to as a calcifying epithelial odontogenic tumors, it has been determined that the amyloid producing odontogenic tumor is not equivalent to the human calcifying epithelial odontogenic tumors. The amyloid producing odontogenic tumors appear as a gingival enlargement which grows by expansion. Clinically the tumors appear similar to a squamous cell carcinoma as they are friable, ulcerated and often bleed easily. Some APOTs are darkly pigmented. It is locally invasive but not metastatic. They occur most commonly in older male cats with a median age of 9 years. It often has a cystic appearance on radiographs. Wide surgical excision is recommended. Complete surgical excision is considered curative.

**Peripheral odontogenic fibroma**
Peripheral odontogenic fibromas now include tumors that were previously classified as fibromatous and ossifying epulides. Peripheral odontogenic fibromas are uncommon in the cat. They can be pedunculated or sessile and may contain osseous material. Complete excision is usually curative.
Non neoplastic proliferative oral lesions

Eosinophilic granuloma
Eosinophilic granuloma can be located on the hard palate, soft palate or base of the tongue. Eosinophilic granulomas are more commonly found in young cats, 2-6 years of age. The etiology is rarely determined and it is often considered idiopathic. Treatment is usually steroids, hypoallergenic diets, RT, surgery, immunomodulation or cryosurgery. The prognosis for complete recovery is fair.

Eosinophilic ulcer
Eosinophilic ulcer is typically a well circumscribed lesion with raised edges and ulceration most frequently located on the upper lip. It is found in cats of all ages and breed, with a higher incidence in middle aged female cats.

Pyogenic granuloma
Pyogenic granuloma is a benign solitary nodules resembling granulation tissue. They are raised, friable and easily bleed. They most commonly occur at the vestibular mucogingival tissues of the mandibular first molar teeth. A pyogenic granuloma can resemble a squamous cell carcinoma clinically.

It is important to keep in mind the less common malignant oral tumors, odontogenic tumors and non-neoplastic proliferative oral lesions in the differential diagnosis list for oral masses as they are often clinically indistinguishable from common malignant oral tumors. A complete evaluation of the patient and the tumor allows the clinician to determine the appropriate treatment recommendations for oral tumors in cats.
Stomatitis is a term used to describe widespread inflammation of the oral cavity. Gingivostomatitis means inflammation of the gingival tissues and oral cavity. Cats with stomatitis may have inflammation or ulceration and/or proliferative lesions anywhere within the oral cavity. The lesions may involve the gingival tissues, alveolar mucosal tissues, caudal buccal mucosal tissues, the area lateral to the palatoglossal folds in the caudal oral cavity, the sublingual tissue and/or the oropharyngeal tissues.

Terms used to describe oral and oropharyngeal inflammation in the feline oral cavity include:

- **Gingivitis**: inflammation of the gingiva
- **Periodontitis**: inflammation of the non-gingival periodontal tissues (periodontal ligament and alveolar bone)
- **Alveolar mucositis**: inflammation of the alveolar mucosa (mucosa overlying the alveolar process and extending from the mucogingival junction without obvious demarcation to the vestibular sulcus and floor of the mouth)
- **Sublingual mucositis**: inflammation of the mucosa on the floor of the mouth
- **Labial / buccal mucositis**: inflammation of the lip / cheek mucosa
- **Caudal mucositis**: inflammation of the mucosa of the caudal oral cavity, bordered medially by the palatoglossal folds and fauces, dorsally by the hard and soft palate and rostrally by the alveolar and buccal mucosa
- **Palatitis**: inflammation of the mucosa covering the hard and soft palate
- **Glossitis**: inflammation of the mucosa of the dorsal and/or ventral tongue surface
- **Cheilitis**: inflammation of the lip (including the mucocutaneous junction area and skin of the lip)
- **Osteomyelitis**: inflammation of the bone and bone marrow
- **Stomatitis**: inflammation of the mucous lining of any of the structures in the mouth; in clinical use the term should be reserved to describe widespread oral inflammation (beyond gingivitis and periodontitis) that may also extend into submucosal tissues (i.e. marked caudal mucositis extending into submucosal tissues may be termed caudal stomatitis).

**Etiology/pathogenesis**

It is thought that stomatitis is a multifactorial disease where the cat’s immune system responds inappropriately to chronic oral antigenic stimulation of various origins. Antigens may include plaque bacteria, feline calicivirus and food proteins. Periodontal disease, tooth resorption, as well as viral infections (FIV, Feleuk, calici, herpes) have been suggested to play a role. Genetic predisposition, food allergies, and bacteria may also play a role in feline oropharyngeal inflammation. Current thought is that cats with feline chronic gingivostomatitis have an inappropriate response or ‘hyper’ immune response to the dental plaque bacteria. Specific bacteria, as seen in periodontal disease, have been reported in these cats. *Pasteurella* and *Prevotella* species are more highly represented than others. Calici virus is present in 97% of cats affected by chronic oropharyngeal inflammation when compared to a control group (25%); however no cause and effect has been established. Some cats with stomatitis test positive for *Bartonella*, but again a cause and effect has not been established. We do not know for sure what causes the disease which makes treatment of the disease challenging.

Cats with chronic gingivostomatitis most often have bilateral disease. Differential diagnoses include eosinophilic granuloma complex, periodontitis, neoplasia (squamous cell carcinoma, fibrosarcoma), uremic stomatitis, caustic chemical ingestion, plant irritation, electrical cord burn, food allergies, and systemic autoimmune diseases (lupus, pemphigus).

**History and clinical signs**

A thorough history is the first step in evaluation of any patient with oral disease. Factors to be considered include the patient’s diet, age at onset of clinical signs, onset and duration of clinical signs, environmental hazards, chronic illness, and / or systemic disease. The median age of affected cats is seven years. No gender predilection has been reported.

Clinical signs may include anorexia, weight loss, hypersalivation, pawing at the face, pain when opening the mouth or yawning, dropping food, and/or reluctance to eat hard food. The patient’s haircoat may be matted and unkempt due to the decrease in self grooming that occurs secondary to oral pain. Halitosis and blood tinged saliva may also be present.

The second step in patient evaluation is a complete physical exam to evaluate all organ systems. A complete intraoral examination will help to determine the extent of disease and identify any teeth with tooth resorption or periodontal disease. A complete examination under general anesthesia including full mouth radiographs is the only way to determine the true extent of oral pathology. Laboratory tests should include a CBC, biochemistry profile, thyroid panel and urinalysis to rule out concurrent systemic disease. A feline leukemia and FIV test should be completed to rule out concurrent viral disease. Many cats with stomatitis will have elevation
of total protein and globulins. Other tests that may be included in the patient evaluation are toxoplasmosis titer, Bartonella screening, viral testing for calici and herpes virus, immune profiles (ANA) and serum protein electrophoresis.

**Treatment**

Feline stomatitis is often a frustrating disease to treat. As there is no known single etiology, treatment success varies with every case. The goal of treatment is to restore the balance between the cat’s immune response and the oral antigen burden. Currently there is no known medical protocol that consistently has positive long term results. Treating with medications usually is only masking the underlying issue of a hyperimmune response to plaque. Extraction of teeth in the vicinity of the alveolar mucositis and caudal stomatitis and extracting teeth with periodontal disease or tooth resorption in order to suppress any chronic oral antigenic stimulation has shown the best results.

The extent of disease at the time of presentation determines the appropriate first stage of treatment. If the patient presents with very mild disease, initial treatment includes periodontal therapy, full mouth radiographs and extraction of any teeth affected by periodontal disease or tooth resorption. The goal of treatment is to remove the bacterial plaque and bacterial byproducts that are toxic to the periodontal tissues with thorough supragingival and subgingival scaling and polishing. It is imperative to remove all inflammation within the oral cavity. Biopsy of affected tissue should be obtained to rule out neoplasia. Histopathology of the mucosa and submucosa reveals dense infiltrates of plasma cells with lesser numbers of lymphocytes, neutrophils and macrophages which is consistent with virtually any inflammation in a cat’s mouth. After the procedure, daily home care is required to maintain a plaque free environment. A chlorhexidine gel applied daily may assist with plaque control. Daily brushing, if the cat will allow it, remains the most effective way to control plaque. In addition to daily brushing, use of Veterinary Oral Health Council (VOHC) accepted diets, treats and/or water additives to control plaque is recommended.

If the owner is unable or unwilling to provide homecare, or if the inflammation persists in spite of home care, or if the inflammation in the oral cavity is moderate to severe, then oral surgery to extract the premolars and molars and/or canines and incisors is recommended. The purpose of extraction is to lower the chronic antigenic stimulation from the plaque bacteria. Traditional medical therapy usually does not control the disease and resolve clinical signs. If there is no visible inflammation in the caudal buccal mucosal tissues or around the canine teeth and incisors then extraction of all of the premolars and molars is recommended. If there is periodontal disease or tooth resorption affecting the canine teeth and/or incisors they are extracted in addition to the premolars and molars. If there is inflammation involving the gingival tissue surrounding the canines and incisors or if there is inflammation in the caudal buccal mucosal tissues then initial oral surgery should be completed to extract all of the teeth.

With oral surgery it is essential to remove the entire tooth root. Full mouth radiographs must be obtained preoperatively. In each quadrant, a mucogingival flap is elevated and buccal bone is removed to expose the furcation of multi-rooted teeth. Each tooth is sectioned and the tooth roots are elevated and extracted. The alveolar bone should be smoothed with a diamond bur (alveoplasty). Each alveolus should be debrided and cleaned with either a diamond bur or hand curette to ensure removal of all tooth, root, and periodontal ligament and bone particles. Following extraction radiographs are obtained to confirm extraction of all tooth roots. NO tooth roots, root fragments or tooth remnants may remain. The periosteum of the flap is released and the alveolar gingival tissue is sutured to the lingual or palatal mucosal tissue utilizing absorbable sutures.

Pre-, intra- and postoperative analgesia is very important in these patients. Utilization of a multimodal preemptive pain management protocol is recommended.

If clinical symptoms persist after extraction of premolars and molars then the author recommends extraction of the remaining incisors and canine teeth to eliminate all plaque retentive surfaces. If inflammation still persists, then adjunctive medical treatment is recommended. Remember, most of these patients have had inflammation for a long time prior to presentation, so the inflammation within the oral cavity is not likely to resolve quickly after surgery. Medications may be necessary for an interim period while the patient’s immune system responds. Frequent periodic monitoring of these patients is required to adjust medications and treatment based on each individual’s response. There are no current studies to support the use of one particular medication over the others as the ‘best’ medical option.

**Medical management of refractory cases**

The primary goal of any treatment for a cat with gingivostomatitis is to decrease inflammation, pain, infection, and to modulate the host’s immune response. Medical treatment is sometimes necessary after oral surgery to control disease in resistant cases.

**Anti-inflammatory drugs**

Use of these drugs as a sole treatment for cases with stomatitis is not recommended. Use of long term steroids can lead to diabetes mellitus and can decrease the body’s ability to resist the inflammatory process. Often with long term use of steroids, cats seem to develop ‘resistance’ and their response to the drug decreases.

Prednisolone - 2 mg/kg daily for a week, then 1 mg/kg daily for a week then a maintenance dose of 0.5-1 mg/kg every other day (goal is to decrease to the lowest effective dose)
Oral triamcinolone - 1.5 mg per cat once daily for a week, then every other day for a week, then every 3 days. Then leave at twice a week for a few months and occasionally try weaning off medication. The pill can be crushed to a powder and suspended in water for administration.

Methylprednisolone acetate 15-20 mg/cat SQ every 3-6 weeks as needed

**Antimicrobials**

Use of antimicrobials will decrease the bacterial load in the oral cavity, but should not be utilized alone in cases of stomatitis. The most commonly used drugs include amoxicillin-clavulinate acid, clindamycin, doxycycline and metronidazole. Azithromycin has been suggested for use in Bartonella positive cats with gingivostomatitis. Studies by Dower and Quimby did not find any correlation between cats with gingivostomatitis and Bartonella and found treatment with azithromycin unrewarding. Chlorhexidine gluconate oral rinses have a bacteriostatic action, though most cats with a painful mouth resist oral rinses. Doxycycline has an inhibitory effect on the secretion of matrix metalloproteinases (which destroy collagen and other matrix components) by gingival PMNs. Use of a submicrobial dose may result in a decrease of gingival collagen destruction. This author has used a dose of 10 mg/cat twice daily for two weeks, then once daily for two weeks, then every other day if the patient shows clinical response. Some patients may require doxycycline at the lowest effective dose forever.

**Immune modulating drugs**

*Cyclosporine* is an immunosuppressant that focuses on cell mediated immune responses. While the exact mechanism of action is unknown, it is believed that it acts by a specific, reversible inhibition of immunocompetent lymphocytes in the G0 or G1 phase of the cell cycles. T-helper lymphocytes are the primary target, but T-suppressor cells are also affected. Lymphokine production and release (including interleukin-2, T-cell growth factor) are also inhibited by cyclosporine. Potential side effects include vomiting, diarrhea, hepatic dysfunction, impaired renal function, anemia, hypertrichosis, and gingival hyperplasia. Monitoring with complete blood counts and biochemistry profiles is recommended. Adjunct treatment with corticosteroids may be necessary.

*Feline recombinant omega interferon* (Virbagen OmegaR, Virbac) are immune modulating cytokines labeled for use in Europe to treat FeLV and/or FIV. It may also be of benefit in acute feline calicivirus infections and FIP. Its principle action is not as a direct anti-viral, but by acting on virus infected cells inhibiting mRNA and translation proteins, thereby inhibiting viral replication. Feline omega interferon has more antiviral effects against certain viruses than human alpha interferon. Virbagen OmegaR has been used in cats that are refractory to traditional treatments for gingivostomatitis. The therapeutic effect of interferon after oromucosal administration is due to the immunomodulatory activity through the oropharyngeal lymphoid tissues and via paracrine activity as this glycoprotein is destroyed during transit through the digestive tract. A randomized double blinded multicenter study was conducted studying calici positive cats presenting with persistent caudal stomatitis after dental extractions. The study showed that treatment with oral feline omega interferon resulted in significant clinical improvement and was found to be at least as good as short term prednisolone therapy in the treatment of calici virus positive cats presenting with caudal stomatitis after dental extractions. Virbagen OmegaR is not currently licensed for use in the US.

**Other medical options**

*Lysine* 250 - 500 mg/cat PO BID Lysine is an amino acid that is thought to compete with arginine for incorporation into many herpes viruses. As it is believed that arginine is required for producing infective virus particles, when lysine is incorporated the virus becomes less infective.

Niacinamide 500 mg ¼ tablet twice daily Used in canine medicine in combination with tetracycline to treat immune mediated skin conditions. It blocks IgE induced histamine release and degranulation of mast cells. When used with tetracycline it may suppress leukocyte chemotaxis secondary to complement activation by antibody antigen complexes. It also inhibits phosphodiesterases and decreases the release of proteases.

**Esterified fatty acids**

Esterified fatty acid complexes are administered orally and work transmucosally to modulate local inflammation.

**Laser treatment**

There is only one case study reporting the use of CO2 laser treatment in a cat with gingivostomatitis. The study concluded that laser therapy is a viable adjunct, but should not be considered as a stand-alone modality or replacement for full mouth or nearly full mouth extractions. The goal of laser treatment is to remove the proliferative tissue to resolve the self-induced trauma and entrapment of food and debris in the tissue pockets; stimulate fibrosis to make the tissues less prone to continued inflammation and proliferation; and reduction of opportunistic bacteria. Laser treatment may also provide some pain relief as the surface nerve endings are cauterized.

**Prognosis**

Hennet studied the effectiveness of dental extractions: 60% of cats were clinically cured; 20% showed significant improvement with minor flare ups; 13% showed only little improvement and required continued medications; and 7% were refractory to treatment showing no improvement. A study of treatment outcome following full mouth extraction published by Girard in 2005 showed 50% resolved without further treatment, 37% improved but required continuing medical treatment and 13% did not improve. There is
continuing discussion regarding which teeth should be extracted - all premolars and molars only or extraction of all teeth (including canine teeth and incisors). There is currently no published data to support either treatment modality.

Owners of cats with stomatitis should understand that not all cats respond to treatment and this disease is often frustrating to treat. It requires consistent treatment and frequent monitoring of the cat’s response to treatment.
Urinalysis – the body fluid of choice for disorders of the urinary tract and more

Collection of urine without contamination (non-urinary chemicals, cells, environmental elements) and without trauma to the urinary tract (which introduces cells and protein into the urine) is critical to the proper interpretation of results. The method by which urine is collected influences the cell and chemical content that will be reported, and should be clearly noted on the urinalysis form. Urine may be collected by voiding, catheterization, or cystocentesis; each method has its own advantages and disadvantages. The single most important kidney function test from the urinalysis is the degree of urine concentration as evaluated by urinary specific gravity (USG). Less than maximal urine concentration may provide clues to underlying renal and endocrine disorders. A complete urinalysis should be submitted whenever serum biochemistry and CBC are submitted in order to allow a clearer analysis of the patient’s condition. Two handbooks/manuals of veterinary urinalysis are available as references.1,2

**Voided urine**

Voided samples are acceptable for evaluation of urinary specific gravity (USG). It is almost never possible to collect mid-stream voided samples from cats. Urine should NOT be expressed from the bladder of cats as trauma from this procedure often adds blood and protein to the sample. Wide fluctuations in USG do not occur throughout the day in cats as occurs in dogs, so timing of sample collection is usually not important. Non-absorbable kitty litter (e.g., Nosorb®) placed in a cleaned and rinsed litter box may allow the collection of a voided sample from cats. Make certain there is no bleach contamination to the sample as this can give an artificially positive reaction for blood on dipstrip chemical analysis. Contamination from the distal urethra, genital tract, skin, and environment can make interpretation of results from voided urine samples difficult. Voided samples are not acceptable for bacterial culture due to the potential for heavy bacterial contamination of the sample from the distal urethra and genital tracts, although the degree of this type of contamination is far less in cats than in dogs. Analysis of a voided urine sample is often needed to determine whether blood observed from a previous sample collected by cystocentesis was caused by the cystocentesis needle.

**Catheterized urine**

It is rarely justified to obtain routine urinalysis by catheter, since the possibility of introducing bacteria is always a threat to create iatrogenic urinary tract infection (UTI). If a urinary catheter is being placed for other reasons, collection of urine through the catheter may be acceptable, but some changes in the urinalysis may be the result of trauma from passing of the catheter. Routine catheterization of male cats should be avoided due to the possibility of causing urethritis and urethral obstruction following the procedure. Culture of catheterized samples may help document urinary infection. Results of urinalysis taken from animals with indwelling urinary catheters are more likely to have blood and protein present, secondary to the presence of the catheter. The initial 1-3 mL of urine from the catheter should be discarded (called a mid-stream catheterized sample), since the first few mL are most likely to be contaminated from the urethra and genital tracts.

**Cystocentesis samples**

In general, it is best to evaluate urine collected by cystocentesis (vesicopuncture), since this method bypasses potential contamination of the specimen with cells, protein, or bacteria from the urethra, vagina, prepuce, and perineum. This is unquestionably the method of choice for urine culture and microscopic evaluation of bacteria in sediment, since normal urine directly from the bladder should not contain any bacteria. Some problems with interpretation of results can occur when the tip of the needle has traumatized the bladder or if the bladder wall has inadvertently been aspirated into the needle during sampling (adding RBC or epithelial cells). Cystocentesis should also be avoided if there has been recent major caudal abdominal trauma due to the possibility of bladder wall devitalization from the trauma.

Cystocentesis is readily performed when the urinary bladder is palpable in cats. If the bladder is not palpable, cystocentesis should not be attempted with blind techniques as used with some success in dogs. Urinary urgency and pollakiuria can make it difficult to keep enough urine in the bladder to obtain a sample from a palpable bladder. It may be necessary to give the cat an analgesic and mild tranquilizer to decrease urgency so that the bladder will fill over the next few hours. Removing the litter tray the night before a first morning appointment increases the chances to be able to palpate the bladder and obtain a cystocentesis sample. This method is useful for cats scheduled to be examined for wellness visits or elective pre-operative procedures.

Sudden collapse following/during cystocentesis has been very uncommonly encountered in cats, probably a result of a vagal-vagal response. Though sometimes dramatic, this effect is quite transient. We have observed this in some male cats with urethral obstruction in which decompressive cystocentesis was very rapidly accomplished. A 22 gauge needle or smaller should be used for puncture of a palpable bladder using dorsal or lateral recumbency. A one-inch needle should be used for thin animals; up to a two inch needle can be used for large or obese cats. The needle should be pointed toward the pelvic inlet to allow collection of a sample as the bladder collapses without needle trauma during aspiration. Although cystocentesis can be performed in cats using dorsal recumbency, it is
safer and easier in most cases to perform the procedure with the cat restrained in lateral recumbency. The bladder can be palpated and isolated using one hand to position the bladder away from the bowel. With four fingers under the cat pull up lightly on the abdomen, using the thumb to isolate the bladder within the abdomen in the ideal position. With the other hand, direct the syringe and needle perpendicular to the body wall, through the abdomen, and into the bladder. Ultrasound (ULS) guidance usually allows cystocentesis of enough urine from a small bladder that could not be sampled during bladder palpation. Even with ULS the bladder may be too small to successfully obtain a sample. In these instances, waiting for the bladder to fill with more urine is advised. In some practices, all urine samples are obtained with ULS guidance whether the bladder is palpable or not. The advantage to this method is that it allows a brief structural evaluation of the bladder to exclude the presence of cystic calculi or bladder masses.

**Performing the urinalysis**

A complete urinalysis that includes evaluation of physical properties, chemical properties, and urinary sediment microscopy should always be performed when possible, otherwise potentially meaningful clinical information will not be evaluated. Acquisition of a very small urine sample volume may not allow the performance of all 3 components of the complete urinalysis, but there is almost always enough volume to analyze the chemical dipstrip and the USG. In some instances all of the small volume will be prioritized to submit for urine culture instead of components of the UA.

Should the UA be performed in-house or shipped to a veterinary referral laboratory? One answer does not fit all practice situations especially depending on technical personnel available and their level of expertise with urinalysis. UA results from fresh urine can differ from those following storage and shipping depending upon time before analysis and temperature conditions of the sample. Samples that sit overnight in the refrigerator before analysis may suffer loss of cells, loss of cellular detail, degradation of casts, and precipitation of crystals that were not there at the time of collection. To lessen the impact of this, an unstained dry mount of urine sediment may be sent along with the urine specimen allowing cellular detail to be preserved (Dr. Maxey Wellman personal communication) but this will not preserve casts or crystals for observation.

A standard quantity of urine should be centrifuged to allow semiquantitative comparison of any abnormal findings between animals or from the same animal over time. Usually 6 to 10 mL is recommended for routine urinalysis, but smaller volumes are often analyzed. The volume of urine subjected to analysis should be specifically noted as used in your practice or sent to a referral laboratory. Comparison of urinary sediment results between large and small urinary volumes that were centrifuged at either high or low speed suggested minimal differences in a recent veterinary abstract but differences in the number of reported of casts were found.

Urinalysis should be performed as quickly as possible following collection of the sample (within 15 to 30 minutes). Prolonged exposure of urine to room temperature before analysis can result in dissolution or degradation of delicate casts, change in pH, growth of bacterial contaminants, and loss of cellular detail due to intracellular degeneration. Refrigeration of the specimen is necessary if examination within 15 to 30 minutes after collection is not possible. The diagnostic value of the urinalysis is greatly enhanced when the urine sample is obtained prior to initiation of diuretic or intravenous fluid therapy that may alter urine concentration. Fresh urine sediment evaluation is likely to be most valuable/revealing in cats that are systemically ill or in the hospital receiving treatment.

USG is the weight of urine compared to that of distilled water. Highly concentrated urine is expected in the urine of healthy cats. USG is the only indicator of renal function in the urinalysis and consequently is very important. USG is estimated by refractometric methods that depend on the bending of light in proportion to the number of molecules dissolved in solution. Refractometers designed for analysis of human urine are often used in veterinary practices, but these have a limited range for the upper scale (1.001 to 1.035). Refractometers designed for veterinary use are more appropriate to use since the scale is calibrated from 1.001 to 1.060. USG most often exceeds 1.035 in cats with normal renal tubular function. It is not acceptable to report USG values as "Greater than 1.035" or "Off the Scale," as potentially valuable quantitative information is lost regarding renal function and risk for idiopathic cystitis or urolithiasis. The refractive index for urine differs between dogs, cats, and humans, so it is best to use a veterinary refractometer that displays different scales to record the refractive index (estimate of USG) for dogs and cats. Both digital and optical refractometry correlate well to urine osmolality, but digital methods remove the variability of subjective interpretation.

Dipstrip reactions for urine chemistry are graded on a subjective scale from 0 to 4 plus, with 1 plus being a trace reaction and 4 plus being the most intense reaction possible. It is important that urine be at room temperature for dipstrip testing as some color reactions are temperature-dependent. Urine should be well-mixed prior to exposure to the dipstrip to ensure that all constituents of the urine will contact the reagent pads. Color reactions should be read in good light, as some of the reactions have subtle color changes, particularly notable for protein content. Highly pigmented urine (obviously bloody or dark with bilirubin) can make it difficult or impossible to accurately determine the degree of color reaction in some instances. Human dipstrip testing for WBC is very unreliable in urine from cats (many false positives). Similarly, dipstrip testing should not be used to determine USG. Automated devices to read the colorimetric reactions from dipsticks are becoming increasingly available in private practice and can remove some of the inherent subjectivity to reading the color reactions with the naked eye.
Evaluation of urinary sediment

The goal of centrifugation is to concentrate otherwise undetectable abnormal urinary elements for microscopic evaluation. A pellet at the bottom may or may not be macroscopically visible following centrifugation. Sedi-Stain® may be added to the sediment to enhance contrast of cellular elements; although this is optional, it is recommended. Sedi-stain sometimes causes mucus strands to look like casts or precipitates to look like bacteria. The microscopic slide is first examined under low power to count casts and to detect areas of interest that need examination under high power. At least 10 high-dry microscopic fields are then evaluated to quantify white blood cells, red blood cells, epithelial cells, and bacteria, and to examine crystals that might be present. Casts are counted per low-dry power field. It is a good idea to bias the examination to include the coverslip margins as elements often accumulate there. It is now easy to capture digital images of urinary sediment using a smart phone and an inexpensive adapter to the microscope eyepiece.11 This allows a more permanent record to be captured and stored for part of the patient’s medical record and also provides a means to send images to specialists for further identification of abnormal elements.

Urinary sediment from healthy animals contains very few cells or casts and no bacteria, but can contain certain crystals. The ability to properly identify red blood cells, white blood cells, and bacteria is most important. Do not expect cells in urine to look like they do on a blood film due to the widely varying effects of urinary osmolality on the cells as well as that from urinary pH and urinary toxins. Highly concentrated urine will cause cells to shrink and very dilute urine will cause cells to swell. The presence of up to 5 red and 5 white blood cells per high-dry microscopic field is considered normal when the sample is obtained atraumatically by catheterization or cystocentesis. Some labs include up to 10 RBC per HPF to be “normal”. Slightly higher numbers of cells (up to 8 red or white cells per HPF) may still be considered normal when a voided sample is examined. The presence of clumps of white blood cells increases the probability that an organism is the cause of pyuria, and clumps should be so noted on the form. Lipiduria is normal in cats – lipid droplets are highly refractile and vary greatly in size. Lipid droplets are often confused with RBC (and sometimes with crystals) but can be differentiated with more certainty following staining with Sudan stain.

Epithelial cells

Zero to occasional transitional epithelial cells should be present in urine from healthy cats. Transitional epithelial cells vary widely in size, and are usually rounded, but only small ones (approximately 1.5 to 2 times the size of white cells) are derived from the kidney. Unfortunately, small transitional epithelial cells can also originate from the lower urinary tract. Small transitional epithelial cells with a tail-like configuration (caudate cells) are thought to arise from the renal pelvis and consequently their presence may suggest upper urinary tract localization of disease. The presence of sheets or clumps (rafts) of transitional epithelial cells strongly suggests neoplasia, but may also occur with severe inflammation. A dry mount cytological preparation of urine should be examined for morphology of these epithelial cells if rafts are consistently identified in the urinary sediment. Squamous epithelial cells can be observed in voided specimens. These cells are of no particular significance in urine as they arise from non-urinary tract tissue.

Bacteria

When urine samples from healthy animals are properly collected and examined in a timely manner, none or very few bacteria should be seen. Particles of debris, stain precipitates, and very tiny crystals may look like cocci when subjected to Brownian motion in urine sediment, resulting in a false positive for bacteria to be reported by the laboratory. It is easier to be confident that bacteria are present when rod-shaped organisms are seen. Specimens which are reported positive for bacteria should be Gram stained or stained with Diff-Quick® for confirmation,12-14 and a quantitative urine culture should be performed. The absence of microscopically visible bacteria does not ensure that bacteria are absent; at least 10,000 rods/mL or 100,000 cocci/mL of urine must be present to be visible during wet-mount microscopy.

Casts

Casts are molds of proteins and cells that form within the lumen of the distal tubule and should be rarely encountered in urine from healthy animals. Cellular casts in urine are always considered pathologic regardless of their quantity. Cellular casts are easily disrupted and can undergo rapid cellular degeneration. So it is essential to examine fresh urinary sediment if cellular casts are to be identified. The presence of cellular casts localizes a pathological process to the kidneys.

Cellular casts may consist of red blood cells, white blood cells, or renal tubular epithelial cells. Red blood cell casts are occasionally observed in acute glomerulitis and following severe renal trauma or renal biopsy. Acute glomerular disease is not common in cats. White blood cell casts (pus casts) are indicative of renal inflammation and are often thought to be caused by bacterial infection. Epithelial cell casts result as the lining of the renal tubule sloughs following a variety of injuries to the kidney – indicating severe tubular injury.

It is easy to identify the type of cellular cast when the morphology of the cells within the cast is well preserved. When cellular degeneration has occurred it can be difficult to tell the difference between white blood cell and epithelial cell casts. Where cell type cannot be accurately determined, the cast is referred to as a degenerating cellular cast. Since even a single cellular cast is of great diagnostic significance, it is important to note their presence. Cellular casts are especially fragile and their presence is easily missed if urine is stored too long prior to examination.
Granular casts are more commonly encountered in animals with renal disease than cellular casts. According to the classic theory of Addis, granular casts develop from degenerating renal epithelial cells, white cells, and red cells that have remained within the renal tubular lumen. Granules can also originate from precipitation of filtered serum proteins into tubular fluid.

Waxy casts consequently require the longest intrarenal time for their development. Waxy casts are translucent and sometimes take up stain intensely. They tend to be brittle, often with visible fractures and sharp, broken off ends. They are not fragile casts, and are stable for some time in alkaline or acid urine. Since it takes more intrarenal time to form this cast, their presence implies local nephron obstruction and often indicates advanced renal disease.

Hyaline casts are pure precipitates of matrix (Tamm-Horsfall) mucoprotein. Hyaline casts are transparent and have low optical density. They can be missed during brightfield microscopy if lighting intensity is not reduced. The presence of persistent hyaline casts usually indicates increased filtration of serum proteins which does not happen in healthy animals. Increased filtered proteins can occur from glomerular disease, passive congestion, and fever. Increased concentration of THP favors its precipitation – this can occur in highly concentrated urine and from increased tubular secretion. Decreased tubular flow rate and the presence of myoglobin or hemoglobin can promote precipitation of THP.

**Crystals**

The presence of crystals in urine is often more confusing than helpful in providing meaningful information. Many amorphous crystals cannot be definitively identified based on morphology alone. Urinary pH can suggest which types of crystals are more like to precipitate out of solution at a particular pH. Crystals can be identified in those without stones, in those with stones, and sometimes in those with stones of another crystal composition, so their clinical significance is questionable in many instances. It is VERY IMPORTANT to remember that crystals can come out of solution after collection of the sample, especially during storage and even more so during refrigeration. Crystals that are reported may not have been there at the time the sample was collected. Struvite crystals are more commonly encountered in small animals. The presence of struvite crystals is commonly encountered in urinalysis from normal dogs and cats. Struvite is easily identified when they assume the “coffin-lid” appearance but they can also assume amorphous forms. Struvite crystals form more often in alkaline urine and are commonly encountered as an artifact following storage and refrigeration.

Calcium oxalate crystals can be helpful in establishing a diagnosis of ethylene glycol (radiator fluid) poisoning in the appropriate clinical setting, but they can also be seen in the urine of healthy animals. So-called "hippurate" crystals also help to support a diagnosis of ethylene glycol poisoning, but they are really not hippurates as was once thought. There are many different morphological appearances for calcium oxalate crystalluria, some of which are not easy to identify. These crystals are more often found in acid urine. The dihydrate form of calcium oxalate is relatively easy to recognize due to its rhomboid shape with internal Maltese cross pattern. Oxalate crystals may be an artifact of storage and refrigeration or may be associated with urolithiasis, hypercalcemia, or ethylene glycol ingestion.

The presence of cystine crystals is abnormal and in animals with urolithiasis does help to confirm their chemical composition. They are usually noted in acid urine. These hexagonal crystals are never normal and are associated with cystinuria or cystine urolithiasis. These crystals may be confused with struvite crystals, but cystine crystals are flat and display little internal architecture.

Urate crystalluria is never normal in the cat. In the presence of confirmed urolithiasis their presence suggests the chemical composition of the urinary stone. The presence of ammonium biurate, leucine, or tyrosine crystals can be seen in animals with liver disease, but are not commonly observed.

Bilirubin crystalluria is never normal in the cat and should prompt further evaluation of liver function.

**Pseudocasts/artifacts**

Sometimes elements within urinary sediment will resemble casts when they are really artifacts, called pseudocasts. The presence of mucus in urine can trap debris in such a way that the resulting structure appears very similar to a cast. The pseudocast can be quite long and its diameter quite variable. Sometimes packing of crystals or many bacteria during centrifugation can produce structures that resemble casts. In these instances, examine a fresh drop of unspun urine for comparison. Squamous epithelial cells have a tendency to roll on themselves and can look like casts, but they are much larger than casts. Degenerated lower urinary tract epithelial cells can produce pseudocasts that resemble granular casts; however, usually these pseudocasts, unlike true casts, have rounded ends and walls which are not parallel.

Vegetative matter such as straw and fiber is observed frequently in specimens collected by voiding. Ova of Capillaria plica can occasionally be encountered in urine sediment of cats with and without signs of lower urinary tract disease.

**Special tips - urinalysis**

- Evaluate fresh sediment- everything is easier to identify
- Crystals from refrigerated urine may be artifacts– note if refrigerated
- Describe if WBC are clumped
• Look closely at clumped WBC for possible organisms
• Describe “bacteria” as cocci or rods
• Don’t rely on dipstrip pads for WBC in dogs or cats
• Don’t rely on dipstrip pads for USG
• If you see things that look like fungal elements, make sure they are not elongate bacteria.
• If fungal elements are seen, make sure they are not in the stain
• Consider Gram-stain of urine when “bacteria” are noted in the urinary sediment.
• Get pH by meter if it is important to know precise values
• Make sure you have the “real” specific gravity – not “off scale”
• Perform dispsticks on urine that has been warmed to room temperature if samples have been stored in the refrigerator
• Be careful to distinguish lipid droplets from RBC in urine from cats
• Quantitate the number of crystals, note if they are aggregating or not, and make sure to report if they were discovered in refrigerated urine

References
Urinary tract infection (UTI) exists when bacteria colonize portions of the urinary tract that are normally sterile (i.e., kidney, ureter, bladder, proximal urethra). UTI most commonly affects the bladder. Bacterial colonization may be superficial along the mucosa, or deeper within the mucosa or submucosa. Bacterial UTI is far less commonly diagnosed in cats compared to dogs and is estimated to affect 1-3% of cats in their lifetime. Dogs with no identifiable anatomical, metabolic, or urinary functional problems of the urethra or bladder can acquire UTI, which is quite different for UTI that develops in most cats. Cats that develop UTI are by definition considered “complicated” since healthy cats have exquisite urinary tract defense systems that simply do not allow a “casual” development of UTI. Cats with bacterial UTI will most often be discovered to have anatomical, metabolic, or functional problems of the bladder or urethra, or have undergone urinary tract instrumentation (e.g., urinary catheterization) that facilitate bacterial ascent and colonization of the urinary tract.

### Diagnosis

Various combinations of hematuria, pyuria, and bacteriuria are observed in urinary sediment from cats with LUT signs associated with a positive quantitative urine culture (clinical UTI). In cats without LUT signs evaluated for other reasons, a positive urine culture in substantial quantity can be documented (occult or asymptomatic UTI – discussed later). The isolation of bacteria in large quantities does not determine whether the UTI is located in the upper or lower urinary tract, if the UTI is chronic or acute, or if the infection is deep within tissue or superficial along the mucosa.

It is important to remember that many particles in urinary sediment from cats, more so than dogs, resemble bacteria – lipid droplets, small crystals, cellular fragments, mucus, stain precipitates. Dry-mount examination of urinary sediment following either Wright’s-Giemsa or Gram stain to further identify bacteria in urinary sediment from cats increases the certainty that UTI really exists or it does not. Urinalysis and aerobic quantitative urine culture reported in colony-forming units per milliliter (cfu/mL) should be conducted in all cats suspected of having a UTI. Isolation of organisms in large quantitative growth (cfu/mL) from a properly collected and handled sample is the gold standard for definitive diagnosis. The number of cfu/mL needed to definitively confirm the existence of UTI varies depending on how the urine is collected and whether clinical signs are present. Lower cfu/mL are often considered clinically significant in patients with increased voiding frequency in which organisms may be eliminated from the bladder before they have time to replicate to higher numbers.

Do not submit sterile swabs soaked or dipped in urine since quantitative culture methods cannot be performed on this type of sample. Culture of urine following cystocentesis is the method of choice to most easily establish a definitive diagnosis of UTI as this bypasses potential contamination with organisms from the distal urethra or genital tract. Far less contamination with bacterial organisms occurs during collection of voided or catheterized urine samples from cats compared to dogs. In 24 samples from healthy cats of both sexes, no growth occurred when urine was collected by cystocentesis. Minimal cfu/mL of bacterial growth occurred from samples collected by urinary catheter. In 9 of 12 samples from male cats no growth occurred; 3 samples grew between 10 and 100 cfu/mL. No growth occurred in 11 of 12 samples from female cats in samples collected by catheter; in 1 sample between 100 and 1,000 cfu/mL growth occurred. Quantitative growth (cfu/mL) was much greater in both male and female cats from urine samples collected by voiding. Organisms grew from all 11 urine samples collected by voiding from male cats. Quantitative growth ranged from 100 to > 100,000 cfu/mL in these samples; in 6 of 11 samples, growth exceeded 1,000 cfu/mL (> 10,000 cfu/mL in 2 samples). No growth occurred in 5 of 12 samples collected by voiding from female cats; in 4 of 7 positive cultures, growth was 1,000 to 10,000 cfu/mL and in 1 > 100,000 cfu/mL. In samples with positive growth, more than one organism was frequently isolated.

True bacterial UTI is likely in cats when ≥ 1,000 cfu/mL of organisms are isolated from urine collected by cystocentesis; < 1,000 cfu/mL is more likely to be from contamination during the collection process. Low-level growth from cystocentesis samples is possible in cats with true UTI when antibacterial treatment has been given recently. UTI is likely to exist when ≥ 1,000 cfu/mL are isolated from urine collected by urinary catheterization from either male or female cats; < 1,000 cfu/mL is most likely associated with contamination. Some criteria state that UTI is likely in cats isolating ≥ 10,000 cfu/mL of bacteria from voided urine, but this may not always be true since high level contamination occasionally occurs in both male and female cats using this method of collection. Culture of voided urine is not recommended since high level contamination can occur from contamination rather than indicating true UTI, though no growth on voided urine samples does provide meaningful information.

The Uricult® Vet dip paddle system (LifeSign, Skillman, NJ) can be a useful in-house screening tool for identification of bacterial growth. Quantitative results (cfu/mL) determined by comparing growth on the paddles with a standard illustration of organism colonies can be a useful in-house screening tool for identification of bacterial growth. Quantitative results (cfu/mL) determined by comparing growth on the paddles with a standard illustration of organism colonies can be used to estimate the bacterial concentration in the urine sample.
density provided by the manufacturer were not always accurate. Inaccuracy in identification of isolated organisms sometimes occurred when paddles were used, particularly when multiple uropathogens were present. This paddle system provides no method for susceptibility testing of isolated organisms, although the bacteria can be categorized into gram-positive or gram-negative status. When growth occurs, paddles or a fresh urine sample should be submitted to a commercial microbiology laboratory for identification and antimicrobial susceptibility testing. Veterinary hospitals should determine whether their referral microbiology laboratory will accept organisms already growing on paddles for definitive identification and minimum inhibitory concentration (MIC) testing. This paddle system for organism isolation appears most clinically useful as an in-house method to identify urine samples that are sterile or samples with low quantitative growth compatible with contamination during the sample collection.6

The Accutest Uriscreen® is an in-house color reaction based test designed to rapidly detect catalase from bacteria and from cells in the urine sample from dogs and cats. A negative test supports that UTI does not exist but there are false positives for UTI, so a positive test necessitates a follow-up quantitative urine culture.7

Organisms isolated from cats with UTI
Twenty-five percent of urine cultures from cats not biased toward those diagnosed with urinary disease were positive for bacterial growth considered indicative of a UTI in one report from a teaching hospital. The criteria to establish a UTI included any growth in a cystocentesis sample, ≥ 1,000 cfu/ml in catherized samples, and ≥ 10,000 cfu/ml in voided urine. The number of cats with true UTI is likely overestimated in this study due to the entry criteria. Eighteen bacterial species were isolated in this study. E. coli accounted for 47% of the isolates, Staphylococcus spp for 18%, and Streptococcus spp for 13%. A single bacterial isolate occurred in 85%; >1 isolate occurred in 15% of the positive cultures. The USG of cats infected with E. coli tended to be < 1.025 whereas those infected with Staph or Strep were usually > 1.025. Older female cats were over represented, as were Siamese cats.8 E. coli and gram positive cocci were also the most commonly isolated organisms from Australian cats with UTI in other reports. Older female cats were also more likely to have a positive urine culture as in the previously mentioned study. E. coli was isolated in 37% of the positive cultures, Enterococcus species in 29%, Staphylococcus felis in 20% and Proteus species in 5%. Enterococcus faecalis accounted for 95% of enterococci spp with the remainder by enterococcus faecium.9,10 Enterococcus accounted for 19% of positive urine culture from cats evaluated at the OSU CVM.11 Staphylococcus felis is a coagulase-negative organism that has traditionally been considered a normal commensal organism from healthy cats present on the skin, eyelid margins, conjunctival sac, and in saliva, but appears that this organism can be a uropathogen for the cat.9

Occult UTI was documented in 38 of 132 urine specimens (44 isolates) collected by cystocentesis from cats without LUT signs, inappropriate urination, or previous UTI – these samples were submitted as part of other diagnostic workups for a variety of conditions including CKD, hypothyroidism, and diabetes mellitus. Hematuria and pyuria were common in the urinalyses from urine culture-positive cats and culture-positive urine specimens were more likely to come from older female cats. Enterococcus faecalis was the most common isolate (19 of 44 total isolates) followed by E. coli (17 of 44 isolates). A few isolates of Proteus mirabilis, Staphylococcus felis, and Streptococcus bovis were also documented in this group of cats. Heavy growth of bacteria at ≥ 100,000 cfu/mL was documented in 39 of 44 isolates and moderate growth at 10,000 to 100,000 cfu/mL was found in 5 of 44 isolates.12 Occult bacteriuria that is either persistent or transient has been described in apparently healthy dogs or those presented for elective surgical procedures13,14 but this has not been reported in healthy cats. Urine was collected by cystocentesis from 108 healthy cats (53 males and 55 females) with a median age of 4.0 years without previous or current LUT signs. Both urine and urine sediment underwent quantitative culture resulting in no growth in 107 of 108 samples. In the remaining sample >100,000 cfu/mL of 2 organisms was isolated, likely the result of contamination.15

A unique form of relapsing UTI is caused by Corynebacterium urealyticum16,17 or corynebacterium jeikeium18 in which encrustations of urinary tissue and struvite (so-called “encrusting cystitis”) prevent eradication of the organism with medical treatment alone. These organisms are rarely isolated as a cause for UTI in cats but may be under-diagnosed. These organisms are often reported as “dipitheroids” thought to be contaminants that are not further characterized. These organisms are often slow growing and require special media to facilitate their growth and identification. These organisms are highly resistant to commonly prescribed urinary antibacterials and the prognosis for cure is generally poor even with surgery and long-term antibiotics.

Conditions associated with UTI in cats
UTI occurs with increased frequency in special populations of cats that include those with metabolic disease (CKD, hyperthyroidism, diabetes mellitus), prior instrumentation of the urinary tract with urinary catheterization, urinary incontinence, acquired anatomical abnormalities (stones, tumors, perineal urethrostomy), and congenital anomalies. Chronic kidney disease (CKD), hyperthyroidism, and/or diabetes mellitus all increase the risk for cats to acquire a true bacterial UTI,19 though clinical signs of UTI may not be present (asymptomatic bacteriuria). In one study 10–15% of cats with hyperthyroidism, diabetes mellitus or chronic renal disease had a bacterial UTI,20 similar to findings of other studies.19-21
In a report comparing 155 cats with UTI to 186 cats without UTI, significant risk factors to acquire UTI were identified for cats with urinary incontinence, transurethral procedures, gastrointestinal diseases, decreased body weight, and decreased urine specific gravity. In this study, 35.5% of cats had no clinical signs associated with their UTI (asymptomatic bacteriuria). UTI in this study was defined as any growth from samples collected by cystocentesis and > 10^3 cfu/mL from samples collected by urethral catheterization. Decreased urinary specific gravity was not identified as a risk for UTI in cats of another study.\textsuperscript{19}

An early report drew attention to the apparently high rate of UTI in cats with azotemic CKD. Five of 15 CKD cat urine samples without obvious bacteriuria in urinary sediment grew organisms and 12 of 19 CKD cats with bacteriuria grew organisms. Whether or not these CKD cats had LUT signs associated with a positive urine culture was not addressed.\textsuperscript{23} The finding of a positive urine culture in cats with CKD could be associated with infection within the kidneys but often this cannot be proven to exist. In a study of 42 female and 44 male cats with CKD undergoing routine urine culture surveillance, positive urine cultures in samples collected by cystocentesis were identified 31 times from 25 cats over a period up to 3 year of their CKD. Eighteen of the 25 cats (72%) were classified as having occult UTI. Eighty-seven percent of cats with positive urine cultures were found to have active urinary sediment. Increasing age was a significant risk factor to acquire occult UTI in female CKD cats. The presence of UTI was not associated with the severity of azotemia or survival in these cats.\textsuperscript{24}

The frequency of UTI in reports of young cats with non-obstructive LUTL signs is quite low (often reported at less than 2%) in most studies in North America, the UK and Europe.\textsuperscript{25,31} Idiopathic/interstitial cystitis accounts for 60 to 70% of diagnoses in cats presenting for some form of urinary urgency. In cats older than 10 years, UTI appeared to be quite common (>50%) in those evaluated for signs of urinary urgency; idiopathic cystitis accounted for only 5% of cases in this group of cats.\textsuperscript{32,33}

A study in 2007 of cats from Norway with a variety of obstructive and non-obstructive causes of LUT signs\textsuperscript{34} found a surprisingly high number of cats with positive urine culture in large quantitative growth, far more so than in other reports. Findings from this study are difficult to interpret since many of the cultures were from voided midstream (46%) or catheterized urine samples (21%) rather than from the gold standard of cystocentesis (21%); in 10% the method of urine collection was not recorded. 44 of 118 samples cultured on the same day isolated bacteria > 10^3 cfu/ml. In 33 of these 44 samples, growth was > 10^4 cfu/ml and in 20 growth was > 10^5 cfu/ml. Quantitative growth from midstream voided samples from healthy cats is sometimes substantial as was shown in 55% of males and 40% of females that grew > 10^5 cfu/ml in another study.\textsuperscript{4}

Congenital anomalies of the urinary tract are occasionally the cause of UTI in young cats. Any condition associated with non-urge related incontinence can be expected to be associated with UTI. A common urogenital sinus malformation was found as the underlying cause for UTI and incontinence in 3 young female cats that were evaluated for recurrent lower urinary tract infections and incontinence (Ohio State University CVM 2014 – publication in preparation). Fusion of the vagina to the proximal urethra created a single vaginourethra. No vestibule existed as the vulva and urethra appeared as a continuous structure that allowed easy fecal contamination. Cystoscopy was the diagnostic tool used in these cases to confirm the abnormal anatomical status. Partial invagination of the urinary bladder was diagnosed in one cat with clinical signs of hematuria, stranguria, and inappropriate urination associated with UTI. This diagnosis may be made on the basis of detection of invaginated tissue in the bladder apex during abdominal ultrasonography.\textsuperscript{35}

**Treatment**

Antibacterial susceptibility testing on isolated organisms is recommended to guide the best treatment selection. Results can reveal the presence of resistance organisms that can predict treatment failure and the need for greater surveillance following treatment. A change in urinary antimicrobial may be needed based on the results of susceptibility testing after the initial treatment was started at the time of submission of the culture.

The Working Group of the International Society for Companion Animal Infectious Diseases (ISCAID) recommends treatment with urinary antibacterial drugs that are likely to be effective against more than 90% of the urinary isolates when this information is available. In general, ISCAID recommends initial therapy for uncomplicated UTI with amoxicillin (11–15 mg/kg PO q8h) or trimethoprim–sulfonamide (TMP-sulfa; 15 mg/kg PO q12h); the group does not recommend amoxicillin–clavulanate for initial treatment in these cases because of lack of evidence for the need for clavulanate in addition to amoxicillin.\textsuperscript{36} Additional detail and a free PDF download of this work published by Veterinary Medicine International is available at [http://www.hindawi.com/journals/vmi/2011/263768/](http://www.hindawi.com/journals/vmi/2011/263768/).

Amoxicillin/clavulanic acid was recommended for Gram-negative infections and amoxicillin for Gram-positive infections in one review of cats with UTI. Variation in bacterial prevalence and susceptibility patterns should also be taken into account when prescribing antibacterial treatment.\textsuperscript{10} Most isolates of *E.coli* in one study showed susceptibility to the 14 antimicrobials tested. *Staphylococcus felis* was susceptible to all antimicrobial agents tested. Enterococcus was universally sensitive to amoxicillin/clavulanic and penicillin/amoxicillin in 2 studies of UTI in cats by the same group.\textsuperscript{9,12} *Enterococcus faealis* can vary greatly in its susceptibility pattern to antimicrobial agents and so may require higher dosage, longer duration or a combination of
therapeutic agents in some patients with overt LUT signs. A high proportion of *Enterococcus* isolates were resistant to clindamycin (97.3%) and cephalothin (72.3%). *Enterococcus* had intermediate susceptibility to enrofloxacin, (61.1%) and marbofloxacin (80.5%). All cephalosporins, potentiated sulfas, and aminoglycosides are notoriously ineffective against *Enterococcus* even when the susceptibility test results return as sensitive for those drugs. *Enterococcus* is usually susceptible to imipenem and meropenem but use of these drugs should be restricted to those cases that have LUT signs and have failed treatment with amoxicillin or amoxicillin-clavulanate. Current recommendations are to NOT treat asymptomatic UTI associated with *enterococcus* since this infection can come and go without treatment. Aggressive treatment for asymptomatic UTI runs the risk that the original *enterococcus* will become more resistant and then become symptomatic when it was not before. There is also the possibility that the *enterococcus* will be eradicated, but UTI with a more virulent and symptomatic organism will take its place.

Resistance patterns were reported for isolates of *E. coli* mostly from urine of dogs (301) and cats (75) in various regions of the United States. Resistance to amoxicillin was 46%, amoxicillin-clavulanate 37%, cefpodoxime 22%, doxycycline 22%, enrofloxacin 21%, trimethoprim-sulfamethoxazole 19%, and gentamicin at 12%. This pattern for *E. coli* resistance suggests that empirical treatment for UTI may have limited success in this geographic location. Treatment of *E. coli* with amoxicillin or with amoxicillin-clavulanate may be less likely to be effective than commonly believed.  

An early report documented the effectiveness of enrofloxacin treatment of UTI in cats. In this study all isolates were considered susceptible to enrofloxacin and post treatment sterility was documented in 21 of 23 cats. As noted above, there are concerns for increasing resistance patterns for *E. coli* in the United States; there are no recent reports of UTI in cats treated with enrofloxacin. The total daily dose of enrofloxacin in cats should be limited to 5 mg/kg either once daily, or divided in order to limit retinal toxicity. Retinal toxicity is a fluoroquinolone class risk, especially for those that achieve the highest retinal concentrations and can result in mydriasis and blindness. It appears that cats as a species have developed a limited efflux mechanism to remove fluoroquinolones from the retina compared to other species. High-dose short-duration protocols prescribing enrofloxacin to treat UTI have been developed for use in dogs with uncomplicated UTI but these protocols should NEVER be used in cats due to retinotoxicity that predictably develops at high doses. Administration of the 3rd generation fluoroquinolone pradofloxacin at 6 to 10 times the recommended dose was shown to have no retinal toxic effects in cats based on rod and cone function evaluated with ERG. Retinal histopathology was unaltered during high dose pradofloxacin treatment. Cats treated with high doses of enrofloxacin showed diffuse retinal degeneration and poor rod and cone function.

Cefovecin is an extended spectrum semi-synthetic 3rd generation cephalosporin approved in Europe for use in cats with UTI caused by *E. coli*, but not approved for this indication in the United States. It is designed to have a 14-day dosing interval after a single subcutaneous injection. Post treatment urine cultures revealed sterile urine in 75.9% of all cats treated with a single injection of cefovecin. *Escherichia coli* was eliminated in 76.7% per cent of cefovecin-treated cats compared with 62.5 per cent of cephalexin-treated cats. Cefovecin demonstrated statistical non-inferiority compared with cephalaxin for bacterial elimination in this study. Efficacy of cefovecin to sterilize the urine in cats with UTI was less than that reported by the same group in dogs with UTI.

Client-owned cats with bacteriologically confirmed UTI were treated with either pradofloxacin, doxycycline, or amoxicillin-clavulanate. Urine culture revealed growth following treatment in 0 of 27 cats treated with pradofloxacin, 3 of 23 cats treated with doxycycline, and in 3 of 28 cats treated with amoxicillin-clavulanate. Pradofloxacin undergoes more hepatic excretion than does enrofloxacin but still achieves urinary concentrations that can be highly effective in the eradication of uropathogens. Pradofloxacin may be the preferred fluoroquinolone to prescribe for use in cats with UTI and impaired renal function due to the hepatic pathway for its excretion and its retinal safety profile should high concentrations of pradofloxacin accumulate in cats with decreased renal function. Pradofloxacin is FDA approved for soft tissue infections in cats; it can be considered for off-label treatment of UTI in cats.

Study of canine and feline *E.coli* isolates that were considered highly resistant to standard antimicrobial agents showed susceptibility to fosfomycin at concentrations well below the susceptible breakpoint. This finding makes it attractive to consider fosfomycin as a treatment for resistant *E. coli*. Fosfomycin is considered a nephroprotectant in some species but in cats this drug can be highly nephrotoxic. When given to experimental cats for as little as 3 days, severe tubular lesions were evident and renal function declined as BUN and serum creatinine increased. The recommendation of 7 to 14 days of an appropriate antimicrobial for treatment of an uncomplicated lower UTI has been based on conventional experience over the years, but surprisingly little data exist to support or refute these protocols. Ultimately, antimicrobials should be given for as long as is necessary to effect a bacteriologically sterile urine during administration of the medication and for a protracted time following discontinuation of treatment.

References
Managing Cats with Idiopathic/Interstitial Cystitis (Parts 1 and 2)
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What is Pandora syndrome?

Is this terminology more helpful than FUS or FLUTD or IC?

Results of studies over the past 20 years indicate that idiopathic/interstitial cystitis in cats is the result of complex interactions between the bladder, nervous system, adrenal glands, husbandry practices, and the environment in which the cat lives. A recent review emphasizes that many cats with a diagnosis of FIC have lower urinary tract- predominant clinical signs that are part of a larger systemic disorder referred to as “Pandora Syndrome”1. Clinical problems outside the lower urinary tract are common in those with a diagnosis of FIC and include signs related to the GI tract, respiratory system, skin, central nervous system, cardiovascular system and the immune system. It has been traditional to refer to cats that have obvious LUT signs as those having “feline urological syndrome”, “feline lower urinary tract disease”, or “feline interstitial cystitis” but this method of naming the disease focuses on the organ with the predominant clinical sign rather than a thorough evaluation of the entire cat and all of its organ systems. A diagnosis of Pandora Syndrome would apply to those cats that exhibit clinical signs in other organ systems (in addition to the LUT), waxing and waning of clinical signs associated with stressful events that presumably activate the stress response system, and undergo resolution of severity of clinical signs following effective environmental enrichment. Currently available evidence suggests that many cases of chronic idiopathic LUT signs presently diagnosed as having FIC actually do have a “Pandora” syndrome. The syndrome might result from early adverse experiences that sensitize the neuraxis to sensory input, increasing the frequency and duration of activation of the stress response system (SRS) when the individual is housed/living in a provocative environment. The chronic “wear and tear” of persistent activation of the SRS can upregulate the inflammatory response in a variety of tissues including the bladder.

Are there different types of presentations for cats with idiopathic/interstitial cystitis?

There are four possible urinary presentations associated with FIC. An acute seemingly self-limiting episode of FIC is thought to be the most common condition presenting to primary care practitioners with an estimated relative prevalence of 80 to 95% (Lulich ACVIM Forum Proceedings Anaheim 2010) – recurrence is likely if stressful situations become severe enough in the future. Frequently recurrent episodes of clinical signs related to FIC is next in occurrence (2 to 15%), followed by persistent forms of FIC (2 to 15%) in which the clinical signs never abate. The fourth possibility is for urethral obstruction to develop in male cats suffering from FIC (15 to 25%). These 4 types of presentations may represent a spectrum of signs from the same disease process, but this hypothesis has not been tested. Most publications reflect data from cats with frequent recurrences or persistent clinical signs that are presented to university referral practices. Based on our data, a potential fifth category could be healthy cats, especially males, that develop LUT signs when when exposed to sufficient stressors2.

What are the differential diagnoses for cats with LUT signs?

Though FIC is the most common diagnosis associated with LUTS in young cats, it is important to exclude the diagnosis of bacterial UTI and urolithiasis in a population of cats with risk factors. Collection of a detailed history that includes queries regarding environmental issues and husbandry practices is an essential first step in deciding if the LUTS are related to irritative voidings or not, and how likely stress may be playing a role. In order to determine if Pandora Syndrome is part of the LUTS, the history and physical examination must be extended beyond that immediately related to the urinary tract. Quantitative urine culture and survey radiography are recommended in the evaluation of all cats with recurrent LUTS to exclude UTI and radiopaque calculi. Advanced imaging that includes contrast radiography, ultrasonography, and urethra-cystoscopy are useful for the exclusion of anatomical defects, radiolucent calculi, and proliferative lesions in some cats.

Figure 1.

Some possible causes of LUTS in cats after appropriate diagnostic evaluation. PE – physical examination; UCS- quantitative urine culture (cfu/ml); Imaging – some combination of radiography, contrast urography, ultrasonography, and/or uroendoscopy. Not all tests are appropriate for every cat, so diagnostic evaluations tailored to each individual cat are most likely to arrive at the correct diagnosis.
What diagnostic workup is needed for cats with LUTS signs?

Figure 2.
A diagnostic approach for cats with LUTS, emphasizing the distinction between those cats that are obstructed or not, and cats that do or do not have irritative voiding.

Can you summarize where we are in our understanding of the pathophysiology of FIC?

Though all the pieces are not completely understood, the basic centerpiece is one of neurogenic inflammation – this type of inflammation is quite different from the standard kind of inflammation classically involving infiltration of neutrophils. Increased bladder permeability is an important part of this process, as this allows constituents of urine to gain access to the bladder wall- these compounds stimulate sensory nerve endings to carry excessive pain signals to the brain. The increase in bladder permeability likely involves changes in the GAG layer and the integrity of the structure and function of the urothelium. The stress response system (SRS) becomes activated but is not adequately terminated by release of cortisol as it is in normal cats. Unrestrained outflow of sympathetic nervous system activity characterizes this disease. Excess effects of norepinephrine are known to upregulate a variety of inflammatory processes including that in the bladder. Infiltration with mast cells is important in some cats with FIC – degranulation of mast cells then contributes to the inflammatory process (vasodilation, edema, diapedesis of RBC, recruitment of sensory nerves with NGF). Local axon reflexes within the bladder wall can result in vasodilation directly, degranulation of mast cells, and detrusor muscle contractions. Certain constituents of urine that gain access to the bladder wall are more potent stimulators of pain than others; absence of some substances in urine can magnify the pain response. The “bottom up” theory emphasizes defects in the bladder wall (GAG and or urothelium that increase permeability) and then over-activation of the noradrenergic nervous system. The “top-down” theory emphasizes that stressors from the environment can be potent enough to directly activate the SRS and turn on neurogenic inflammation³. Another piece of the pathophysiology is that cats with FIC appear to have mild adrenal insufficiency based on a blunted increase in cortisol concentration following ACTH stimulation compared to normal cats. The adrenal glands of cats are also smaller than those of normal cats and do not contain histopathologic lesions ⁴. One explanation proposes that these small hypofunctioning adrenal glands are the result of a maternal perception of threat that is transmitted to the fetus from hormones that cross the placenta to effect the development of the fetal adrenal gland at a critical time for its development. ⁵ It should be emphasized that only adrenocortical steroid measured was that of cortisol, and that many other adrenocorticosteroids have the potential to also be deficient⁶, but this has not yet been studied in cats. Cats with idiopathic cystitis do not appear to experience long-term benefit from current glucocorticoid therapy regimens. The same in utero developmental story just described could also account for a fetal stress response that has been programmed toward enhanced vigilance that would then be manifested after birth by an intense SRS output when the cat faces provocateurs. FIC cats in colony housing have higher levels of circulating catecholamines and their metabolites compared to normal cats, especially when exposed to a stressful environment. A return to lower levels of circulating catecholamines occurred in stressed FIC cats following environmental modification, but this response was less complete and took longer than that which occurred in healthy cats ⁷. FIC cats were recently reported to have a heightened response to sensory stimuli when measured by the acoustic startle reflex (ASR) compared to healthy cats ⁸. The ASR is a defensive brainstem mediated response to sudden intense stimuli. Environmental enrichment led to a significant decrease in ASR in cats with IC compared to healthy cats. Habituation to new housing prior to environmental enrichment decreased ASR in female but not male cats with FIC⁹. Results of this study add to the concept that management of FIC benefits the cat when the patient’s perception of unpredictability in the environment is reduced. Urodynamic evaluation of female cats with FIC revealed no finding of spontaneous detrusor muscle contraction that can occur in overactive bladder (OAB) further separating FIC from OAB ¹⁰. Consequently, drugs that target detrusor muscle contraction do not appear warranted in cats with FIC. High maximal urethral closure pressure (MUCP) was documented in female cats with FIC of the same study, suggesting that alpha-1 –adrenoceptor antagonists, alpha-2 agonists, or skeletal muscle relaxants could potentially be useful treatment ¹¹ but this has yet to be studied.
Sensory neurons (C-Fiber) seem to play a central role in transmission of action potentials via the dorsal root ganglia (DRG) to the spinal cord (SC) and brain. These signals may be perceived as painful by the brain. Sensory fibers also can propagate a local axon reflex without transmission of an axon potential. The axon reflex results in release of peptide neurotransmitters such as substance P (SP) by the nerve endings. Interaction of SP with receptors on vessel walls results in vascular leakage, which can be augmented by SP-induced release of histamine by mast cells. These actions may give rise to the submucosal petechial hemorrhages (glomerulations) observed at cystoscopy. Receptors for SP also occur on smooth muscle, which when activated stimulate muscle contraction. Also shown are the urothelium (epithelium) and the overlying glycosaminoglycan (GAG) layer adjacent to the bladder lumen. Damage or malfunction of either or both of these layers may permit constituents of the urine, such as protons, potassium ions, or hyperosmolar (>2,000 mOsm/L) fluid to activate the sensory fibers. The effects of stress on sensory fibers may be related to descending efferent sympathetic (SNS) signals stimulating the DRG and inducing peripheral release of neuropeptides. Local release of neurotransmitters by bladder sympathetic fibers also could stimulate sensory fibers. Another factor probably involved in chronic, neurogenic inflammation of the bladder, but not shown, is local and systemic release of nerve growth factors, which may promote sensory fiber terminal sprouting to increase the size of sensory fiber receptive fields.

**Is there a role for pheromonotherapy in treatment of FIC?**

Feline facial pheromones (FFP) are commercially available (Feliway®) with the listed indication to decrease urinary spraying and marking. Activation of the sympathetic nervous system is part of the vigilance system that results in urinary spraying and marking and it is thought that these products lower the intensity of sympathetic nervous system output. Since unrestrained output of sympathetic nervous system activity is a central component in neurogenic inflammation that occurs in FIC, it seems reasonable that use of FFP could also be useful for treatment of FIC. In one study of hospitalized healthy and sick cats videography was used to score behavior and food intake of cats in which the cage was pre-treated with vehicle placebo or feline facial pheromones. Increased grooming, facial rubbing, interest in food, and walking were found in cats exposed to FFP compared to vehicle. Results of this study suggested that hospitalized cats exposed to FFP were calmer and more comfortable in their cages than cats exposed to vehicle. It has been our observation that some cats are very affected by FFP while in others the effect is minimal to nil. A randomized, double-blinded, placebo-controlled, crossover study was performed in 12 cats (9 of 12 completed the full study) with recurrent FIC, comparing once daily environmental treatment with FFP (Feliway®) or placebo; treatment was for 2 months and then switched to the other treatment for the next 2 months. This small number of cats exposed to FFP had fewer mean days displaying signs of cystitis, a reduced number of episodes of cystitis, and fewer negative behavioral traits, but this data did not achieve statistical significance for a difference over placebo treatment of the environment.
Is there a role for amitriptyline or other tricyclic anti-depressant (or analgesic) TCA for the treatment of FIC?

In some cases YES. The need for this kind of therapy has dramatically lessened since we as a profession have become much more successful at implementing environmental modification, which usually works well without need for chronic drug therapy. We do prescribe amitriptyline for its beneficial effects for cats with FIC that have frequent recurrences or persistent LUT signs AFTER the client’s best efforts to implement environmental enrichment have failed to improve the cat’s clinical signs. This type of therapy should NOT be undertaken for an initial episode of FIC or a “flare” of signs that occur infrequently. We sometimes prescribe amitriptyline for cats owned by clients that are considering euthanasia for their cat with FIC – this can sometimes allow the client to see early benefits while implementing environmental enrichment. Maximal beneficial effects of TCA, if any, often require weeks to months to be observed and in general should not be abruptly discontinued (so called “abrupt withdrawal syndrome”). Treatment series of FIC with amitriptyline has been reported 3 times, 1 study of chronic FIC (frequently recurrent or persistent signs) and 2 of acute bouts of FIC. In the chronic study, 15 cats were enrolled with FIC that failed to respond to other treatments; no placebo group was treated. Amitriptyline treatment (10 mg PO every 24 hours in the evening) successfully decreased clinical signs of severe recurrent FIC in 9 of 15 cats treated for 12 months (11 of 15 cats for the first 6 months). Somnolence, weight gain, decreased grooming, and transient cystic calculi were observed during treatment in some cats. Despite clinical improvement, cystoscopic abnormalities persisted in all cats at the 6- and 12-month evaluations. In one short term study, 31 untreated male and female cats with acute (<14 days signs), nonobstructive, idiopathic lower urinary tract disease were enrolled in a placebo controlled study. Cats were hospitalized and treated with 5mg amitriptyline or a placebo daily for 7 days and then treatment discontinued. Clinical signs and hematuria resolved similarly in both groups of treated cats by day 8. Cats were evaluated in the clinic 1 month later and by questions over the telephone 6, 12, and 24 months after treatment. Clinical signs recurred faster and more frequently (10.5 vs. 2.4 events/1,000 days) in the amitriptyline treated cats, a finding likely attributable to the abrupt withdrawal of amitriptyline treatments after 7 days- there was no difference in recurrence when the first 21 days were excluded from the analysis. In another short-term study of FIC, amitriptyline at 10 mg once daily per os (11) or placebo (13) was given for 7 days by owners at home. All cats were also treated with amoxicillin BID for 7 days. The severity of clinical signs was assessed at days 0, 7, and 14 – no significant difference was found between amitriptyline and placebo treated cats of this study.

How do we treat an acute episode of LUT signs for either its first time, or an infrequently recurrent event?

We treat nearly all FIC cats of this type with a combination of buprenorphine and acepromazine PO for 5 to 7 days. The combination of an analgesic and a tranquilizer with properties that also decrease urethral tone seem like a compassionate and appropriate choice of treatment. It is likely that the tranquilizer reduces the activity of the autonomic nervous system which is useful in the initial treatment of FIC. We believe that this helps to acutely decrease clinical signs in cats with acute episodes of FIC or flares of chronic FIC, though this has not been specifically studied. Whether this regimen reduces future episodes of FIC has also not been tested. We take the opportunity at the first visit to discuss with the owners that even a first event of FIC may be associated with recurrence and that there may be steps that can be taken to reduce this likelihood (not yet studied in a prospective way) when environmental enrichment and modification are successfully implemented.

What analgesic treatments should I consider?

The best approach to analgesia for bladder pain (visceral) has yet to be determined. Butorphanol has been used, but its effects are less long-lived or potent than those of buprenorphine. Sustained release formulations of buprenorphine have recently become available that can provide up to 72 hours of therapeutically drug levels for pain relief following a single injection. Fentanyl patches have been used in rare cases in which bladder pain was assessed as severe. Should I consider NSAID treatment to provide anti-inflammatory and analgesic effects?

Anecdotal reports of the usefulness of non-steroidal anti-inflammatory drugs (NSAID)s, especially meloxicam and ketoprofen, abound, but no studies of safety or effectiveness are available for review. Some specialists have prescribed piroxicam for use on alternate days, but there are no controlled clinical trials of its effectiveness or safety. NSAIDs are not commonly used for treatment of interstitial cystitis in humans. NSAIDs that are licensed for use in cats list indications for pre-emptive pain management, usually as a single treatment before anesthesia and surgery. Chronic use of NSAIDs in cats can be dangerous due to the possibility for development of acute intrinsic renal failure; especially should the cat become dehydrated for any reason at the time of NSAID administration. The FDA recently required the following statement to be added to the label for meloxicam use in cats, “Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. See Contraindications, Warnings, and Precautions for detailed information.” Robenacoxib, a long acting NSAID recently has become available for use in cats; its effectiveness and safety for use in cats with FIC has yet to be reported to our knowledge.

What is the most-important therapy to recommend to owners of cats with frequently recurrent or persistent signs of FIC?

There is no simple answer to this question but a key component to a successful outcome is empowering the owner with skills that allow the cat’s husbandry to be improved and the environment enriched to a point that decreases the cat’s stress response system. We refer you to the Indoor Cat Initiative site that is maintained by Dr. Buffington- this site provides a great number of details and resources that can be considered to implement that will reduce the cat’s perception of stress and improve its general sense of well

375
being while living largely in confined spaces with people (and often with dogs too). Environmental enrichment involves effective resource management, including; litter box (es) (type, location, number, resting areas, opportunities to climb and scratch, interactions with people that are positive, and methods to reduce conflict in the living space with other cats, dogs, and humans \textsuperscript{22-24}. Outcome of environmental enrichment and modification was proven beneficial to most FIC cats of a study in which they had failed multiple other treatments \textsuperscript{25}. In addition to a dramatic increase in the use of the litterbox, there were benefits in behavior and some gastrointestinal signs.

**Is there anything new regarding dietary treatment of FIC?**

A non-blinded and non-randomized study of feeding canned vs. dry diets of similar formulation (Waltham pH Control\textregistered{}) in the treatment of 54 FIC showed a beneficial effect of the canned over the dry product \textsuperscript{26}. 52 of 54 cats exhibited more than one episode of LUT signs in the prior 12 months. The study lasted for 12 months, or until signs of recurrence occurred. Signs of LUTD did not recur in 16 of 18 cats fed the canned diet, and 17 of 28 cats fed the dry diet (\(P < 0.05\)). The recurrence rate in cats being fed the dry food was also reduced compared to the rate encountered in the previous year, but not to the degree of benefit observed in cats consuming the wet formulation. The mean urinary specific gravity was lower in urine from cats fed the canned formulation but the basis for the salutary effect of this particular canned product over the dry formulation was not determined \textsuperscript{26}. Other factors that could have influenced results of this study include hedonics (the mouth feel of the food) or the ritual associated with the feeding of canned foods and this effect on cat behaviors. The consumption of dry foods is known as a risk factor for the development of LUT disease in cats on a dose-related basis \textsuperscript{27}. The results of a test food vs control food as treatment of FIC was recently reported as an abstract in 31 cats over 12 months. The test food contained more anti-oxidants and omega-3 dietary oil than the control food as the main difference. The feeding of the wet or dry formulation was determined by owner preference. The number of episodes for LUT signs and days exhibiting LUT signs (1.3 vs. 10.3 events/1000 days) were fewer in cats fed the test food of this study. Outcome was the same during the feeding of either the wet or dry formulations of the test food\textsuperscript{28}. The event rate for the test diet was not significantly different from the same author’s previously reported event rate in untreated cats \textsuperscript{18}; the basis for the effect of the control or test formulations in this study was not determined. The test diet is not available commercially, as the original diet was altered to include stress-reducing compounds for the commercial diet that was launched but this specific formulation was not studied.

**How important are non-specific therapeutic responses in treatment of FIC?**

Nonspecific therapeutic responses might occur during treatment of cats with FIC, possibly by altering their perception of their surroundings as part of a placebo-response. The effectiveness of environmental enrichment suggests that pharmacological or other therapeutic interventions face an important barrier to demonstrate efficacy in the presence of the large therapeutic response to this approach in cats with the syndrome.

**Figure 5.**

What do WE Do? Step-wise approach to treatment of cats with idiopathic lower urinary tract signs. More diagnostics should be performed when cats fail to spontaneously clear of their initial lower urinary tract signs and when signs recur to ensure that the diagnosis is really idiopathic lower urinary tract disease. Properly controlled clinical trials may provide better approaches to treatment in the future, but this is what we do in the interim.

**“Pearls” Pandora syndrome – aka feline interstitial/idiopathic cystitis (FIC)**

1. Signs of urinary urgency during FIC may be expressions of a systemic disease created by a highly active outflow (unrestrained) from the sympathetic nervous system in response to stressors (provocateurs).
2. When multi-modal environmental modification (including environmental enrichment) is effectively implemented, treatment with drugs is RARELY NEEDED.
3. Stress up-regulates the inflammatory potential of several organs, including the bladder.
4. Bacterial urinary infections (UTI) are rarely identified in cats with signs of lower urinary tract disease, unless they have specific risk factors (U-cath within last 6 months, perineal urethrostomy, dilute urine – CKD, diabetes mellitus, hyperthyroidism)
5. The term “Pandora Syndrome” should help to remind the clinician that LUT signs may be part of a bigger picture that involves other organ systems.
6. We advocate the use of analgesia (buprenorphine) during acute episodes of FIC.
7. We use tranquilization with acepromazine in combination with buprenorphine in most of our cases of non-obstructive episodes.
8. On occasion, the use of amitriptyline can be useful in the treatment of FIC.
9. The use of GAG (glycosaminoglycan) supplementation has failed to show an effect superior to placebo in several studies of FIC treatment.
10. The use of feline facial pheromones has not been shown to be superior to placebo in the treatment of FIC.
11. The feeding of as much wet food as possible in the diet is advocated by some for its protective effect on the recurrence of the signs of FIC, and may be helpful as long as it does not result in additional threat to the cat.
12. There is no indication for surgery in non-obstructive FIC.
13. When surgery is performed in patients with FIC, obtain a full thickness bladder biopsy to allow evaluation of mast cells with special stains (toluidine blue).
14. Sometimes a so-called “placebo” treatment actually can have a positive effect between the cat, the owner, and the environment such that a positive outcome is achieved.
15. In most cases, antibiotic treatment does not have a role in the treatment of FIC.
16. Treatment of FIC with glucocorticosteroids has not shown an effect greater than that of placebo in limited study.
17. Chronic treatment of FIC with NSAIDs is NOT ADVOCATED due to the high sensitivity of the cat to sustain renal injury with this class of drugs, especially if there is any tendency toward dehydration.

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Buffington CA. External and internal influences on disease risk in cats. Journal of the American Veterinary Medical Association 2002;220:994-1002.
Pathophysiology of urethral obstruction (UO)

Thrity-nine % to 67% of male cats evaluated with lower urinary tract signs have been reported to have urethral obstruction.¹⁴ Male cats with urethral obstruction (UO) were described to have urethral plugs as the most common cause in early reports,³ but recent reports emphasize idiopathic causes.¹²⁵ In one study the cause of obstruction was considered to be idiopathic in all 82 cats studied,⁶ but other studies report plugs, urolithiasis and UTI in decreasing order behind idiopathic causes for UO.¹¹²⁵ When plugs do form, it is likely that they are extensions of the process leading to feline idiopathic/interstitial cystitis (FIC). This is consistent with findings from an unpublished study at The Ohio State University using urethroscopy at the time of initial evaluation in which plugs were rarely identified. Urethral plugs have minimal intrinsic cohesive structure but often are cylinder-shaped after extrusion from the urethra. Urethral plugs are fundamentally different from calculi that lodge within the urethra (i.e., urethroliths). Uroliths have an organized internal structure with much less matrix, and are not easily compressed or distorted. Urethral plugs consist largely of matrix mucoprotein with embedded minerals. The predominant mineral composition in most plugs is magnesium ammonium phosphate hexahydrate (i.e., struvite). This is true despite the fact that cats form calcium oxalate and struvite uroliths with nearly equal frequency. Most plugs are assumed to lodge within the penile urethra, but obstructions also can occur at more proximal sites. Definitive diagnosis of a urethral plug requires retrieval of the plug. Supportive evidence for the presence of a urethral plug can be seen on radiographs in some cats with UO. Previously, the crystalline-matrix hypothesis proposed that plugs formed secondary to precipitation of struvite crystals in the urine that then became embedded in a matrix. According to this hypothesis, plugs created UO and urethritis. It is now hypothesized that plugs form as a consequence of underlying idiopathic urethritis and cystitis (i.e., inflammation occurs first, followed by plug formation).

Some cats have signs of non-obstructive idiopathic/interstitial cystitis before UO, while many cats have lower urinary tract signs after relief of UO. Obstruction can be secondary to functional urethral spasm in addition to swelling of the urethra due to edema and hemorrhage. Pathologic or neurogenic processes cause contraction of the circular smooth or skeletal muscle of the urethra or both. Stimulation of adrenoreceptors (particularly α-1) within the urethra increases urethral tone in normal cats. Pain and stress after UO increase sympathetic outflow from the central nervous system which can lead to additional urethral spasm.

Bacterial urinary tract infection (UTI) is very uncommon before urethral catheterization.³⁷ UTI deserves more consideration in cats with recurrent UO that have undergone urinary instrumentation. Urethral strictures may occur, especially in cats that have had previous indwelling urinary catheters and for those with severe recurrent episodes of non-obstructive idiopathic/interstitial cystitis. Neoplasia of the urethra or bladder neck is rare. Urinary catheter fragment foreign body in urethra or bladder is rare, as is phimosis as a cause for UO.

Signalment, history, physical examination

Approximately 75% of cats presented with UO are experiencing their first episode.⁶⁸ Median duration of clinical signs before initial presentation was 3 days in a study of 223 cats. Signs include those of cystitis and partial obstruction before development of complete obstruction. The majority of cats with UO are relatively stable however, approximately 10% are critically ill.

Severe bradycardia (< 100 bpm) from the effects of hyperkalemia has been reported in 5% of cases, moderate bradycardia (100-140 bpm) in 6% of cases and mild bradycardia (140-160 bpm) in 12% of cases; arrhythmias were detected in 11% of cases. Fifty % of cats can be expected to have normal body temperature, hypothermia in about 40% and hyperthermia in 10%. Rectal temperature < 95-96.6°F or heart rate < 120 bpm was the most the accurate predictor of severe hyperkalemia. A combination of hypothermia and bradycardia was 98 to 100% predictive for severe hyperkalemia (> 8.0 mEq/L).³ Nine or seizures is very uncommon (0.5%) and related to ionized hypocalcemia. Systemic blood pressure most often is normal.¹⁰ Mean arterial pressure correlated inversely with serum potassium and directly with total serum calcium concentrations. Major abnormalities on physical examination and serum biochemistry were encountered despite normal blood pressure in this study.

Diagnostics

A recent report noted that darker red urine observed at the time of urinary catheter placement was associated with azotemia, hyperkalemia, and lower USG. Color of the urine was not associated with the presence or absence of urinary stones.¹¹ Hyperkalemia does not occur in isolation and often is accompanied by acidosis and low serum ionized calcium concentration. Serum potassium concentrations ranged from 3.4 to 10.5 mEq/L in 199 cats. Six % were below the reference range; 41% were above the reference range, and 53% in the reference range. Serum potassium concentration was < 6.0 mEq/L in 66% of cases, > 6.0 but < 8.0 mEq/L in 12% of cases, > 8.0 but < 10.0 mEq/L in 12% of cases, and > 10.0 mEq/L in < 1% of cases. Hyperkalemia most often was encountered with acidosis (pH < 7.2 in 74% of cases) and low serum ionized calcium concentration (< 1.0 mmol/L in 75% of cases).
Approximately 33% of cats with UO are expected to have clinically relevant hypocalcemia based on serum ionized calcium concentration. Serum ionized calcium concentration was below the reference range in 34%, above the reference range in 19%, and in the reference range in 47%. Serum ionized calcium concentration was > 1.2 mmol/L (> 4.8 mg/dL) in 23%, > 1.0 but < 1.2 mmol/L (> 4.0 but < 4.7 mg/dL) in 57%, > 0.8 but < 1.0 mmol/L (> 3.2 but < 4.0 mg/dL) in 14%, ≤ 0.8 mmol/L (≤ 3.2 mg/dL) in 6%. Serum total calcium concentration in 51 cats was below the reference range in 39%, above the reference range in 0%, and within the reference range in 61%. Cats with low serum total calcium concentrations had moderate to severely decreased serum ionized calcium concentrations.\(^5\) In one study, more cats were found to have hypocalcemia when defined by measurement of serum ionized calcium concentration (75%) than when defined by serum total calcium concentration (27%).\(^12\) Survival of cats with UO was influenced by ionized calcium status in another study. The median concentration of ionized calcium in survivors was 1.08 mmol/l (range 0.65 to 1.28 mmol/L) and in non-survivors was 0.88 mmol/l (0.66 to 1.11 mmol/L); \(P = 0.037\). Hypocalcemia was detected in 51% of survivors vs 100% of non-survivors; \(P = 0.024\).\(^6\)

Struvite crystals may be observed at the time of obstruction, especially if urine pH is alkaline. The presence and amount of struvite crystalluria preceding UO has not been reported. Struvite crystalluria can be expected from any condition associated with urinary pH increased above 6.7. Crystals are more likely to be secondary to urine stasis or alkaline urine pH (secondary to sterile inflammation with extravasation of plasma proteins into urine) than a primary cause of obstruction. Struvite crystalluria was greater in male cats with obstruction than in male cats without obstruction (\(P = 0.051\)), though cause or effect of the crystalluria was not established in one study. Struvite crystalluria was not associated with hematuria, proteinuria, or pyuria but was associated with urinary pH in this same study.\(^5\)

Nearly all cats with UO have sterile urine on original presentation for obstruction. Zero of 18 cats with UO in one study\(^7\) and in 0/36 cats in another study soon to be published out of The Ohio State University (Dr. Ed Cooper OSU - personal communication 2014) had bacterial growth. Bacteria were isolated from urine collected through the urinary catheter at initial presentation in 14% of cats (14/192) in one study, but quantitative methods as to cfu/mL were not used. Many of these cats were referred with an indwelling urinary catheter already in place.\(^13\) Only 1 of 32 cats in another study had a positive urine culture from a cystocentesis sample at the time of UO relief.\(^14\) Bacterial culture at the time of urinary catheter removal is more likely to identify pathogenic bacteria. Isolation of bacteria from cats with a previous history of UO is more likely than isolation from cats suffering an initial episode.

**Imaging of cats during/after UO**

All cats with UO should have radiography to determine if urolithiasis is contributing to obstruction. Attention is usually centered to determine the presence of urinary stones in the bladder and/or urethra. It is very important to include the perineal region in the radiographs to identify urethral calculi. Evaluation of the kidneys and ureters is important to be sure nephroliths or ureteroliths are not part of the overall process, because upper urinary tract involvement can markedly affect the overall prognosis. Free fluid resulting in a loss of abdominal detail can be seen in some cats with severely distended and highly permeable (“leaky”) urinary bladders. A small amount of free abdominal fluid may be identified at initial presentation that is more easily detected on ultrasonography. In cats with recurrent UO, contrast radiography and ultrasonography may be informative as to the underlying diagnosis. Positive contrast urethrogramy is especially useful to disclose urethral trauma, urethral perforation, or urethral stricture, especially after recent instrumentation of the urethra. Radiography is the gold standard imaging method for the detection of urethral stones as ultrasonography only examines the most proximal portion of the urethra. If only ultrasonography is available to image the urinary tract (limitations of equipment, personnel, or cost), then it is advisable to perform the sonogram before AND after reverse flushing of the urethra in order to detect the presence of small stones that may now appear in the bladder after hydropulsion that were not initially visible. This however does not exclude the presence of stones still within the urethra.

Caudal abdominal effusion was detected in 10 of 34 cats on radiographs after placement of a urethral catheter without associated cystocentesis.\(^15\) Nineteen of 34 cats with UO that underwent abdominal radiography had signs of abdominal effusion before or after cystocentesis and passage of a urinary catheter. Prior to cystocentesis, 11 of 20 cats had abdominal effusion in the same study.\(^14\) In another study in which therapeutic cystocentesis was used as the sole treatment to relieve bladder pressure, 8 of 15 had evidence for abdominal effusion after bladder pressure was first relieved.\(^16\) In yet another study, 87 cats underwent abdominal ultrasonography within 24 hours of the relief of UO by passage of a urethral catheter and no use of cystocentesis.\(^17\) Hyperechogenic pericystic fat and pericystic effusion were each observed in 60% of these cats. Ninety % of evaluated cats had bladder thickening, 20% had suspended linear strands, and over 50% of cats had either moderate or severe increases in urinary sediment or hyperechogenicity. Cystolithiasis was documented in 47% of these cats. This frequency is much higher than that in another report in which only 2 of 35 cats were found to have stones (radiography in 34 cats and ultrasonography in 3 cats).\(^14\) The reason for this disparity between ULS and radiography in detection in cystolithiasis is not obvious. ULS could be more sensitive in the detection of uroliths, but ultrasonography and radiography has not been compared in the same cats with UO at the same time of their clinical presentation, before or after instrumentation. It is also possible that more stones were detected in the study using ultrasonography since these images were acquired.
after urethral flushing which could have retropulsed urethral stones into the bladder. Eight cats with pseudomembranous cystitis associated with UO have been described in two reports.\textsuperscript{17,18} Thick echogenic septa were described traversing the bladder lumen. These bands could represent sloughing of necrotic areas of the bladder into the lumen and they were associated with fibrinous exudate, blood clots, and necrotic debris.

It has long been taught that acute UO in male cats adversely affects renal function but does not create structural changes in the kidneys. It has been known for decades that palpably enlarged kidneys are detected during physical examination in some cats before relief of UO. In cats with UO undergoing ultrasonography, either unilateral or bilateral renomegaly was detected in 42\%, pyelectasia in 60 \%(10\% > 3.4 mm), and perirenal effusion (retroperitoneal) in 35\% of the cases. Ureteral dilatation was detected in 24\%. How rapidly these changes resolve has not yet been reported.\textsuperscript{17}

**Relief of obstruction due to plugs or idiopathic causes**

Decompressive (therapeutic) cystocentesis is the next step recommended to perform after sedation and IV catheter placement. The benefits of decompressive cystocentesis outweigh potential adverse effects. Decompressive cystocentesis has been considered controversial by some clinicians who fear that bladder rupture will occur or that urine will continue to leak from the bladder. No adverse effects were observed in a recent report of 47 UO male cats that underwent decompressive cystocentesis.\textsuperscript{19} Cystocentesis to empty the bladder should be performed as soon as possible in cats with very large bladders to prevent rupture of the bladder and to allow renal excretory function to resume. Cystocentesis allows for rapid reduction of urinary tract pressure and resumption of GFR compared to catheterization, which can take considerable time. Decompressive cystocentesis may stabilize the cat before anesthesia for urinary catheter placement. Relief of bladder pressure before urethral catheterization also may facilitate efforts to dislodge urethral plugs, and allows collection of a superior urine sample for analysis before manipulation of the urinary tract and contamination by irrigation solutions.

Some leakage of urine immediately after decompressive cystocentesis may occur, especially if the bladder is not adequately emptied. The use of a 22-gauge needle on an extension set or use of a butterfly needle can minimize trauma and urine leakage during the procedure. In one study, the median volume of urine removed by urinary catheter at the time initial obstruction was relieved in 28 cats was 85 mL (range, 35 to 280 mL).\textsuperscript{10} Plain abdominal radiographs (including the perineal region) should be obtained after decompressive cystocentesis to identify mineralized plugs, urethral calculi, or cystic calculi. Some clinicians obtain radiographs after catheter passage, but the presence of an indwelling urinary catheter can obscure the presence of urethral calculi.

Standard epidural techniques require special expertise and training but a new simplified method using sacro-coccygeal placement of local anesthetic to allow urethral catheterization and pain management appears promising.\textsuperscript{19} This technique produces anesthesia to the perineum, penis, urethra, colon, and anus within 5 minutes of preservative-free lidocaine injection and lasts up to 60 minutes. The authors of this study concluded that relief of urethral obstruction was easier and quicker during placement of the urethral catheter, presumably associated with urethral relaxation. Cats of this study received pre-medication protocols but not full anesthesia. Cats did not appear to struggle during catheterization, flushing, or suturing after the lidocaine infusion and appeared to be less painful after catheter placement.

Studies in cats have shown that indwelling polyvinyl catheters create less urethral trauma and inflammation than do indwelling polypropylene catheters. Silicone urinary catheters have not been specifically studied in cats. Do not administer glucocorticoids to a cat while an indwelling urinary catheter is in place. The risk for bacterial pyelonephritis is great in this setting and glucocorticoids are unlikely to control urethritis in this setting (i.e. continuous trauma from an indwelling catheter).\textsuperscript{20} The use of antibiotics does not prevent the development of UTI in patients with indwelling urinary catheters. Do not prescribe antibiotics while a urinary catheter is in place (unless you have documented by bacterial culture that a UTI already is present). Antibiotic use may promote development of resistant isolates when UTI does develop. Consider culturing the urine when the urinary catheter is removed. This recommendation is supported by the finding that 6 of 18 cats developed significant bacteriuria (3/6 at 24 hours and another 3/6 at 48 hours) within 48 hours while the indwelling urinary catheter was in place.\textsuperscript{7} Recurrent UO at day 30 was significantly less common when the indwelling urinary catheter was left in place for more hours, though the median times were similar between those with recurrence and those that did not recur.\textsuperscript{15}

The chronic prognosis for recurrence of LUTD signs following relief of UO is guarded. Eight of 22 (36\%) cats with idiopathic UO re-obstructed after a median of 17 days in one study whereas 3 of 7 (43\%) cats with UO associated with urethral plugs re-obstructed within 7 months. Recurrent obstruction was the cause for euthanasia in 21\% of cats in this study.\textsuperscript{2} The recurrence rate was 22\% at 6 months and 24\% at 2 years.\textsuperscript{6} Ten of 68 cats were reported to developed recurrent UO within 30 days of release from the hospital in another study.\textsuperscript{15} In an older study, the recurrence rate was 35\% within 6 months.\textsuperscript{21} No studies on recurrence rates for UO have been reported prospectively after implementation of aggressive environmental modification. Recurrence rates may be lower in cats for which environmental modification can be adequately implemented. A small number of cats develop urethral strictures. This is a complication that occurred in 11\% of affected cats in one study.\textsuperscript{22} Some cats develop bacterial UTI after instrumentation of their
Non-conventional treatment for urethral obstruction in male cats

Non-invasive non-instrumentation treatment protocol

A report describing a method for relief of urethral obstruction in male cats without the use of urethral catheterization was recently described. The reported treatment protocol was proposed for use only as an alternative to euthanasia due to financial constraints of owners unable to afford conventional treatment costs. Conventional treatment with passage of a urinary catheter and IV fluid infusion in the hospital was offered as the first choice. This non-invasive approach is not meant for cats with urethral calculi or those with severe metabolic derangements. The severity of azotemia does not determine use of this protocol. A plain lateral abdominal radiograph is taken to exclude calculi. Decompressive cystocentesis is performed initially and then as needed up to every 8 hours. The urethra is not irrigated or catheterized, though the distal penis is gently massaged. No IV catheter is placed and IV fluids are not administered. Drug treatments include: acepromazine (0.25 mg IM or 2.5 mg PO q8h), buprenorphine (0.075 mg PO q8h), medetomidine (0.1mg IM q24h if no urinations are noted in the first 24 hours). The cat is placed in a quiet, low stress environment. Some fluids may be given subcutaneously as needed, but the goal is to avoid excessive urine production from full hydration. Treatment success was defined as spontaneous urination within 72 hours and subsequent discharge from the hospital. Successful discharge from the hospital occurred in 11/15 cats (73%). Treatment failure occurred in 4/15 (27%) cats due to uroabdomen (3) or hemoabdomen (1). Cats that experienced treatment failure had significantly higher serum creatinine concentrations. At necropsy, severe bladder inflammation was found, but there was no evidence of bladder rupture.

**Atracurium**

The intraurethral installation of atracurium besylate was compared to that of physiological saline prior to retrograde flushing of the urethra. Atracurium besylate is a curare derivative that provides neuromuscular blockade of striated muscles by antagonizing acetylcholine at the nicotinic receptor in the neuromuscular junction. Atracurium besylate is rapidly inactivated by plasma esterases or by spontaneous degradation and does not depend on the liver or kidneys for excretion. Atracurium was first diluted from 10 mg/dl to 0.5 mg/dl and then injected under steady gentle pressure for 5 minutes while the external urethral orifice was occluded. Sixty-four percent of cats treated with atracurium were unobstructed during the first hydropulsion attempt compared to 15% of cats receiving the saline installation prior to flushing. The mean time to relieve obstruction was 21 seconds in those receiving atracurium compared to 235 seconds for those receiving the saline control.

**Lidocaine**

The recurrence rate and clinical signs for UO in 26 cats were determined at 2 weeks, 1 month, and 2 months following intravesical installation of lidocaine vs placebo once daily for 3 days through the indwelling urinary catheter. The recurrence rate for obstruction (58% [7/12] in the lidocaine group and 57% [8/14]) in the control group and magnitude of clinical signs were not different between treatment groups.

**Prazosin vs phenoxybenzamine**

In a recent report of UO cats, overall recurrent obstruction at 24 hours occurred in 21/192 cats (10.9%) and at 30 days in 37/157 (23.6%) cats. The recurrence rate in cats treated with prazosin was 10/140 (7.1%) and 20/110 (18.8%) at 24 hours and 30 days following urinary catheter removal compared to 10/46 (21.74%) at 24 hours and 16/41 (39.02%) at 30 days in cats treated with phenoxybenzamine, which was different statistically. Recurrent urethral obstruction is most likely to occur within the first 7 days following urinary catheter removal in most studies. Recurrent urethral obstruction occurred within the first 4 days of urinary catheter removal in 32 of 37 (86.49%) male cats in this study. The use of a 3.5 Fr indwelling urethral catheter was associated with less recurrent obstruction at 24 hours following removal of the urethral catheter compared to the use of a 5.0 Fr indwelling urinary catheter. The logic for the use of prazosin in the treatment of male cats with UO was challenged by one group on the basis that this drug blocks alpha receptors of urethral smooth muscle and that the obstruction usually involves the penile urethra which is surrounded by striated muscle. We seemingly have also had success using drugs that are designed to block peripheral alpha adrenoceptors – there could be central nervous system effects that have yet to be studied in cats. It is also possible that there is “cross-talk” between the autonomic nerves and those controlling somatic tone to the urethra. Another possibility for a salutary effect could be some “downstream” effect on the striated muscle after tone in the smooth muscle is reduced.

**Intravesical GAG treatment**

A proprietary GAG formulation designed for intravesical administration has recently been manufactured by Arthrodynamics and marketed as A-CYST® from Dechra Veterinary Products. This formulation consists of 5 mg/mL of hyaluronic acid and 100 mg/mL of chondroitin sulfates (C4 and C6) in a 10% solution of n-acetyl-d-glucosamine (NAG). The commercial preparation designed for
intravesical installation was studied for its safety when administered IM (0.1 mL/lb) to 8 healthy cats every 4 days for a total of 5 treatments. No systemic toxicity was observed and decreased oxidative stress was suggested based on one measured marker.26 Sixteen male cats with acute urethral obstruction were enrolled in a randomized placebo controlled study comparing this GAG treatment to that of placebo installations.27 After relief of urethral obstruction, the bladder was flushed to remove debris. After residual urine was removed, either the GAG preparation or saline placebo was instilled (2.5 mL) through the indwelling urethral catheter at times 0, 12, and 24 hours after placement of the indwelling urethral catheter. Saline or GAG solution was kept in contact with the bladder for 30 minutes prior to allowing urine to flow through the collection system again. All cats were followed for 7 days following removal of the urethral catheter the time of which varied to the individual cat’s needs. Acute repeat obstruction occurred in 0/9 cats treated with the GAG preparation and in 3/7 cats treated with the saline placebo (P = 0.06). Two of the 3 cats that failed placebo treatment were crossed-over to enter the GAG treatment group to contribute to the final 9 cats in this group that did not reobstruct. No adverse effects were identified following intravesical infusion of either the GAG or saline solutions.27 Though the GAG treatment group did not achieve statistical significance, zero cats treated with the GAG solution had recurrence of UO during the 7 days of this study. Further study is warranted to see how the data emerges in a larger series of cats with UO that are treated with this treatment protocol.

Amitriptyline

A report from Brazil suggests that oral amitriptyline may be useful in relief of UO in male cats caused by urethral plugs.28 Obstructed cats had serum creatinine concentrations of > 4.0 mg/dL and BUN concentrations of >120 mg/dL before treatment. Treatment details were not provided in this publication but were obtained by me from the author with the help of a Portuguese-speaking translator (2009). Some cats had decompressive cystocentesis performed and all were given IV 0.9% NaCl. No cats had urethral flushing or placement of an indwelling urinary catheter. No other drugs or anesthetic agents were administered besides ampicillin for prevention of UTI. This protocol has been used in Dr. Achar’s practice as the standard of care for many years. Amitriptyline (1 mg/kg) was given orally for 30 days. This time period was arbitrarily chosen to decrease the likelihood of recurrence of UO. Amitriptyline should never be abruptly discontinued because of possible development of “abrupt withdrawal syndrome.” Urethral plugs were spontaneously eliminated and urinary flow was restored in all cats within 72 hours. Urethral plugs were analyzed and found to contain varying proportions of struvite, calcium oxalate, and ammonium urates. Transient somnolence was attributed to the use of amitriptyline, an effect that lessened as azotemia resolved. This effect has been described when amitriptyline is used in cats without azotemia. All cats had normal BUN and serum creatinine concentrations when measured 30 days later. No cats experienced recurrent UO during the 30 days of treatment. The beneficial effects of amitriptyline in cats with UO appear to be mediated by relaxation of urinary tract smooth muscle through mechanisms that involve voltage-dependent potassium channels.

References

Acute kidney disease in cats: diagnosing, managing, and preventing

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Acute kidney injury (AKI) is the term used to describe a spectrum of acute alterations in kidney function and structure that range from mild (clinically inapparent) to overt acute renal failure (varying degrees of azotemia). Portions of the nephron may be temporarily injured or they may sustain lethal injury resulting in permanent loss of nephron mass depending on the severity of the insult. Recovery of full renal function and histopathological structure is possible in some cases. Partial recovery with substantial nephron loss will result in recovery as a CKD patient in some. In other patients, severe injury results in substantial loss of nephron mass and renal function that will not allow a reasonable quality of life without dialysis. Severely azotemic AKI patients often require dialysis to be managed adequately.

The details of a new grading system for categorization of acute kidney injury (AKI) developed by IRIS (International Renal Interest Society) are available for further review at http://www.iris-kidney.com/guidelines/grading.shtml. Much like the IRIS staging system for CKD, this grading system is designed to detect AKI at early stages when it is more likely that therapeutic interventions can avert further injury and allow recovery of renal function and tissue repair. The clinical prognosis is likely to align with the AKI grade that develops. Historically, attention was mostly directed to patients with serum creatinine that exceeded the reference range. In the IRIS AKI scheme, even a small increase in serum creatinine within the reference range is considered an important marker for potential acute renal injury. The IRIS AKI grading system involves evaluation of fasting serum creatinine concentration as the first step and then the staging is refined based on urine output if it is known (see Table 1). The same cutoffs for creatinine and urine output have been chosen for use in the dog and the cat. Oliguria, normal urine production, or polyuria can all occur depending on the specific cause and severity of renal injury sustained during AKI. History and physical examination parameters also enter into assignment of the grade. AKI typically focuses on those with acute injury to kidneys that were intrinsically normal prior to the acute injury. Pre-renal and post-renal disorders can occur in the absence of primary renal injury but they can also occur on top of a primary renal injury. Patients with CKD often have an “acute-on-chronic” presentation with changes in level of azotemia that falls into the AKI grading scheme. An inability to regulate solute and water balance is often present and renal synthetic and degradatory functions are impaired to varying degrees during AKI. It should be noted that this AKI staging scheme is dynamic in that the grade may increase or decrease in severity over time and treatment. Extensive diagnostic evaluation may be needed to determine the specific cause(s)/diagnosis underlying the AKI; specific diagnosis is not specified by the AKI grading status.

Differential diagnosis and frequency of AKI – See Table 2. Causes of AKI in cats

The frequency of underlying conditions associated with AKI varies with the nature of the veterinary practice. Nephrotoxicity is the leading cause for AKI at The Ohio State University Veterinary Hospital, followed by ischemia. The aggressive use of potentially nephrotoxic antibiotics, particularly the aminoglycosides, can contribute to nephrotoxic AKI. The exposure to cholecalciferol rodenticides, use of non-steroidal anti-inflammatory drugs (NSAID), and exposure of veterinary patients to extensive surgical procedures and aggressive post-traumatic resuscitative maneuvers as emergency patients can result in AKI. Ischemic and nephrotoxic AKI occur more readily in patients that have underlying chronic renal disease or renal failure.

Diagnosis of AKI

Rapid increases of BUN, serum creatinine, and serum phosphorus may be observed during severe AKI. This is particularly helpful to document AKI in the absence of recent serum biochemistry values for comparison. For example, a patient’s serum creatinine of 4.3 mg/dl, 6.0 mg/dl, and 7.5 mg/dl sequentially over three consecutive days supports a diagnosis of azotemic AKI. Serum creatinine and BUN do not increase over this short a time period in hydrated patients with CKD. Hyperphosphatemia may be out of proportion to the degree of increase in BUN or serum creatinine in those with AKI compared to CKD. The magnitude of elevation in BUN or serum creatinine concentrations is not helpful in the diagnosis of azotemic AKI vs CKD or in the differentiation of pre-renal, intrinsic renal, or post-renal azotemia. See Table 1 AKI grading for how to detect AKI at earlier levels of increasing serum creatinine. Urinalysis reveals a low specific gravity (USG) during the maintenance phase of azotemic AKI (SG less than 1.030, but most-often in the 1.007 to 1.015 range). Decreased maximal USG may be detected before an increase in serum creatinine is detected. Dipstrips may show proteinuria, hematuria or glucosuria on occasion. UPC can be increased due to increase in protein excretion normally handled by renal tubules. Urinary sediment is typically “active” at early stages of the maintenance phase of severe AKI exhibiting increased numbers of casts (particularly cellular casts) and small epithelial cells compatible with renal tubular epithelium. Animals with AKI as the sole problem should have smooth kidneys with normal or increased kidney size whereas those with chronic renal failure may show small and or irregular kidneys both on palpation and abdominal radiographs. Renal ultrasonography can provide additional anatomic...
information to confirm intrarenal lesions, but cannot be relied on to distinguish acute from chronic renal failure or to suggest a specific microscopic lesion. Failure to document ultrasonographic renal changes does not exclude a diagnosis of AKI. Kidneys may enlarge during AKI but this may not be detected if they are still within the normal range for kidney size; kidneys tend to become “plump” before they measure elongated. Peri-renal effusion was described in 6 cats with azotemic AKI. Renal biopsy may be helpful to determine that an azotemia is due to primary renal lesions and to characterize the changes as acute or chronic. A positive urine culture in the face of AKI is of concern for upper urinary tract infection, but this finding alone is not definitive to establish a diagnosis of pyelonephritis.

It is imperative to exclude acute post-renal azotemia due to ureteral stones or stricture in cats presenting with azotemia that appears to have developed suddenly. In some cats ureteral stones cause complete obstruction of one or both ureters resulting in varying degree of oliguria or anuria and rapidly escalating magnitude of azotemia. Due to the frequency of this syndrome associated with calcium oxalate urolithiasis, survey radiographs need to be evaluated in all cats suspected to have AKI. If renal or ureteral stones are noted, ultrasonography to determine the degree of any hydronephrosis and or hydroureter is the next step. Many of these cats have pre-existing chronic kidney disease that makes it relatively easy for azotemia to develop even when only one ureter is obstructed. In many instances, there is the presence of “big-kidney little-kidney” syndrome likely reflecting previous chronic kidney injury reducing the size of one kidney and hydronephrosis increasing the size of the second kidney. Though the azotemia can be quite striking and rapid in development, these cases represent acute post-renal azotemia on top of chronic primary kidney disease. Medical therapy is not often successful in management of these cats and relief of the ureteral obstruction by minimally invasive stenting or traditional surgery will be needed in order to sustain life without dialysis. The prognosis following relief of the obstruction is often guarded due to the underlying chronic kidney disease.

**Prognosis of AKI**

The attending veterinarian and client often have greater expectations for immediate improvement following treatment than is realistic, remembering that the maintenance phase of azotemic AKI can last weeks in some cases before adequate renal repair and function can occur. The most likely causes for death during the initial management of the azotemic AKI patient in the maintenance phase are from the effects of hyperkalemia, metabolic acidosis, and severe azotemia. Overhydration and resulting pulmonary edema are the next major causes of death during vigorous fluid therapy.

There is no magnitude of increased serum creatinine concentration measured at one time point that determines prognosis. Serial serum creatinine measurements over time are much more informative. Acute changes in the concentration of serum creatinine were associated with prognosis in one study of 209 cats with an initial serum creatinine of < 1.6 mg/dl and at least 2 serum creatinine measurements within 7 days. A poorer prognosis was found in cats that increased their highest serum creatinine to > 1.6 mg/dl with at least an increase of 0.3 mg/dl. If this increase in serum creatinine were achieved within 3 or 7 days, cats were about 3 times more likely to die at 30 days and 4 times more likely to die within 7 days. When this increase in serum creatinine occurred within 2 or 3 days, death within 90 days was 3 times more likely. Azotemic AKI was diagnosed in 32 cats of an earlier study (serum creatinine >2.5 mg/dl); 18 cats were oliguric at the time of diagnosis. About half of these AKI cats survived (53%) with complete resolution of azotemia in 25% and persistent azotemia (CKD recovery) in 28%. The initial BUN or serum creatinine concentration did not predict survival nor did oliguria. Serum potassium increases seemed to be the most important predictor of survival; a 57% decreased chance in survival occurred for each mEq/L increase over the initial serum potassium concentration. Low initial serum albumin and bicarbonate were also associated with less survival.

A grave prognosis is warranted for cats that develop anuric AKI after IV fluid treatment, a situation most-likely to develop in ethylene glycol intoxication but may also be encountered in cats following ingestion of Easter or day lilies. It should be noted that dogs and cats with severe oliguric AKI have recently been shown to survive with return of renal function and urine production following several months of hemodialysis. The presence of non-oliguria does not guarantee survival either. Due to the poor to grave prognosis for many cases with severely azotemic AKI, prevention is far preferred to treatment.

**General goals for treatment of azotemic AKI during the maintenance phase**

Placement of an indwelling intravenous catheter is necessary to adequately administer fluids and drugs in the management of azotemic AKI. Rapid correction of dehydration is indicated and can be individually calculated (estimated % dehydration x body weight in kg = Liters of dehydration) or given as 2 to 3 times maintenance fluid needs (60 to 90 ml / pound per day). Further fluids are given to match sensible (urinary volume), insensible (respiratory losses at about 10 ml/lb/day),and contemporary (an estimated volume from vomiting and diarrhea) fluid losses. Since urine output is widely variable in AKI, it is advisable to place an indwelling urinary catheter to monitor urine output to facilitate fluid therapy decisions for the initial 24 to 48 hours. The recognition of oliguria is important initially as it dictates the volume of IV fluid therapy that can be safely given. Urine production less than 1.0 ml/kg/hour (24 ml/kg/day) qualifies for oliguria in our hospital prior to rehydration and volume expansion. Relative oliguria exists if urine production is form 1.0 to 2.0 ml/kg/hour while on IV fluids. Urine output should be from 2.0 to 5.0 ml/kg/hour during vigorous administration of
IV fluids if the kidneys are healthy. It is essential to curtail the fluid prescription for volume to be further infused once hydration has been established especially when urine output does not increase. It is the author’s impression that it is easier for cats with AKI to develop overhydration compared to dogs with AKI even with careful monitoring.

**Newer thinking about the dangers of IV fluid therapy in the critically ill**

If insufficient fluids are given to the AKI patient, the kidneys are not optimally perfused and sustain further ischemic injury. If too much fluid is given, then overt overhydration with pulmonary edema, congestive heart failure, and death follow. A new paradigm suggests that too many fluids and subclinical development of overhydration also result in further renal injury from visceral overhydration and reductions in renal blood flow and GFR as renal interstitial edema develops. Renal edema can be an early development following some forms of renal injury. It appears that renal edema can also develop as a consequence of too aggressive fluid therapy. Conventional wisdom has been that it is better to have a little over-hydration than to have the damaged kidneys endure any chance for underperfusion and ischemic injury. It now appears that contrary to popular opinion, it is better to be a little on the “dry” side following rehydration and moderate resuscitation rather than to risk the development of over-hydration. It is possible that declining renal functions in the face of aggressive fluid therapy (reflected by rising BUN, creatinine, and phosphorus) may actually be caused by this treatment and resulting renal edema. Interstitial edema decreases renal blood flow by compression of renal vessels, and opposes GFR by compression of Bowman’s capsule and compression of renal tubules. This concept needs to be further evaluated in both human and veterinary medicine. For now, caution is advised so that minimal fluids following correction of hypotension and rehydration are administered. The concept that “less is more” has been advocated in a veterinary review of AKI in cats.

**Conversion from oliguria to non-oliguria**

Mannitol, furosemide, dopamine, or combinations of these are the diuretics most often employed in attempts to convert oliguria to non-oliguria or to increase renal function (RBF, GFR). Rehydration prior to use of diuretics should occur first to allow greater delivery of the diuretic to its site of action. There are no reports that detail the response of cats or dogs with clinical AKI to these treatments. The so-called “renal-dose” of dopamine (below the vasopressor dose, often from 2 to 5 micrograms/kg/minute) has surprisingly little clinical documentation to support its use in either human or veterinary medicine. A combined infusion of dopamine and furosemide to awake normal cats increased urine output but did not increase GFR. Fenoldopam as a selective DA-1 receptor agonist has the potential to cause renal vasodilatation with increased RBF, GFR, and natriuresis without activation of alpha and beta adrenergic receptor effects that occur with dopamine at higher doses.

**Ethylene glycol nephrotoxicity**

The gold standard to prove the presence of ethylene glycol or its toxic metabolites following bioconversion remains testing with HPLC on serum or plasma samples. This type of testing is not commonly available, though it can be performed at local human hospital laboratories. The EG Test Kit (Allelic Biosystems, Kearnesville WV) is supposed to be able to detect 50 mg/dl of ethylene glycol in a serum/plasma sample but this has not been studied in cats. Test strips designed to detect ethylene glycol (Kacey ethylene glycol test, Kacey Inc, Asheville, NC.) were found to have too many false positives and false negatives to be useful for clinical work in cats. The Catachem test kit (Catachem Inc., Oxford, Connecticut) detected the presence of EG when added to serum or plasma of dogs and cats but did have a positive bias in slightly overestimating actual EG concentrations. This company provides both a quantitative and qualitative test to detect EG. The utility of the osmole gap has been ignored by many in the critical care community. A large osmole gap is proportional to the amount of unmetabolized ethylene glycol in many cases. A large osmole gap is most commonly created by ethylene glycol ingestion in small animals, but a large osmole gap could also result in animals that have consumed propylene glycol as an alternate and less toxic formulation of antifreeze. The presence of calcium oxalate crystalluria is supportive for the diagnosis of ethylene glycol intoxication in the appropriate setting – cat that is sick, possible history or observation of ingestion, and sub-maximally concentrated urine. Calcium oxalate crystalluria is observed in fewer cats than in dogs with ethylene glycol intoxication. Calcium oxalate monohydrate crystalluria is more commonly detected than calcium oxalate dihydrate crystal following EG ingestion. Calcium oxalate monohydrate has several different morphologic appearances that can be difficult to identify whereas calcium oxalate dehydrate is more easily recognized. An extremely hyperechogenic renal cortex and medulla may be observed soon after ingestion of lethal quantities of EG in the cat as in the dog.

Fomepizole at high doses is the antidote of choice to treat cats following EG ingestion. Fomepizole is administered in higher doses than needed in dogs in order to effectively inhibit alcohol dehydrogenase, which otherwise is the first step in the bioactivation of EG to its toxic intermediary metabolites. Fomepizole is given to cats with an initial dose of 125 mg/kg IV followed by 31.25 mg/kg at 12, 24, and 36 hours. Use of this treatment protocol was effective in prevention of azotemic AKI in experimental cats treated within 3 hours of exposure to an otherwise lethal dose of EG. Fomepizole was a more effective treatment than ethyl alcohol and provided less CNS depression (some sedation was observed). This fomepizole protocol was successfully used to treat 3 cats with naturally occurring EG poisoning that were not azotemic at presentation. If fomepazole is not available and it is within 3 hours of EG
ingestion, 20% ethanol at 5mL/kg IV initially, followed by the same dose every 6 hours for 5 treatments and then every 8 hours for 4 treatments could be a life-saving alternative antidote. Ethyl alcohol should ALWAYS BE DILUTED prior to administration, otherwise IV administration can cause cardiac arrest.

**Lily nephrotoxicity** 28-32

The cat is exquisitely and perhaps uniquely sensitive to the nephrotoxic effects following lily ingestion. The specific toxic principle is unknown but all parts of the lily are toxic to cats. Nephrotoxicity has been observed in cats that have chewed only a small portion of a single lily leaf. The Lilium genus contains nearly 100 species and hundreds of hybrids that are thought to be toxic too. Aqueous extracts of the flower and leaf from the Easter lily contain the toxic principle, with the flower being more potent. Calla lily and peace lily are not real lilies and are not associated with AKI in cats. Lily of the valley does not contain a nephrotoxin, but does contain a digitalis-like toxin. Pancreatic histopathology is observed in some cats.

A history that the cat was observed chewing on lily plants or the finding of fragments of the plant observed in the cat’s vomitus provides pivotal clues to the diagnosis. Hypersalivation and vomiting may occur soon after ingestion of lilies due to local irritant effects on the GI tract. Vomiting and lethargy are commonly described 1 to 5 days after plant ingestion in those suffering AKI. Renomegaly and abdominal pain may be detected on physical examination. Varying degrees of azotemia may be documented in cats presenting days after lily ingestion. On urinalysis, isosthenuria, proteinuria, glucosuria, cylindruria, and occasionally ketonuria are present in those with severe AKI but crystalluria is notably absent. Oliguria or anuria may persist despite intravenous fluid therapy in those with severe AKI.

Decontamination combined with fluid diuresis for 48 hours prevents development of azotemic AKI for up to 6 hours after ingestion of lilies. Decontamination 18 hours or more after lily ingestion does not prevent development of azotemic AKI. Induction of vomiting followed by administration of activated charcoal and a cathartic is recommended by the Animal Poison Control Center. Vomiting should not be induced in cats that already are vomiting as a consequence of lily ingestion. No antidote is available to counteract effects of the absorbed nephrotoxin. Nearly all cats presented early with GI signs alone survive after decontamination and induction of diuresis.

As many as 33% to 50% of cats that ingest lilies will develop azotemic AKI if not treated within a few hours following lily ingestion. Anuric AKI can occur 18 to 24 hours after ingestion. Prognosis for recovery is poor after lily-induced development of severely azotemic AKI. The magnitude of azotemia that develops during AKI does not predict survival, but urine output does. Cats with azotemic AKI that are polyuric are more likely to survive. Cats with azotemic AKI and persistent oliguria or anuria are unlikely to survive. Cats that survive severe azotemic AKI after lily ingestion tend to have substantial permanent loss of renal mass and go on to develop various stages of CKD.

In a recent abstract, 30 cats were treated for lily ingestion associated AKI and 22 cats survived. Eighteen of the 30 cats were managed with aggressive medical treatment in which 89% survived. Twelve of the 30 cats were treated with intermittent hemodialysis with a 50% survival rate. Urine output and hydration status at time of diagnosis were not related to survival. Cats with a serum creatinine > 2.0 mg/dl at the time of diagnosis were more likely to die. 33

**NSAID AKI**

NSAIDs are not directly nephrotoxic, but rather work as nephrotoxicants that cause their damaging effect through intense vasoconstriction that develops under special circumstances. NSAID cause AKI only if systemic vasoconstrictor signals have been activated following hemodynamic insult (sodium depletion, volume contraction, hypotension, shock, anesthesia). Normal renal vascular resistance and renal blood flow are relatively well maintained during times of vasoconstriction if synthesis of renal vasodilator substances is normal. Renal vasoconstriction however proceeds unopposed if the synthesis of renal vasodilatory prostaglandins has been blocked by NSAID administration. In these instances, progression to acute azotemic AKI and papillary necrosis may occur. An increased frequency of azotemic AKI was reported in 16 young cats given NSAID at the time of routine desexing without IV fluid administration. Four of these cats were euthanized due to failure of severe azotemia to resolve, 4 cats survived with azotemic CKD, and 8 cats recovered with complete resolution of azotemia. 34 In 21 cats with NSAID AKI of another study, the mortality rate was 25% mostly in cats associated with papillary necrosis. Supportive therapy for up to 4 weeks was required for some survivors. 35 The FDA recently required the following statement to be added to the label for meloxicam use in cats, “Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats…” Robenacoxib, a long acting NSAID, recently has become available for use in cats in North America. Whether the incidence of NSAID-associated AKI is less during treatment with newer generation NSAIDs touted to have less GI side effects remains to be determined.
Table 1. IRIS AKI grading criteria – 2013 guidelines
Each grade is sub-graded as non-oliguric (NO) or oligoanuric (O) and if needing renal replacement therapy (RRT)

<table>
<thead>
<tr>
<th>AKI Grade</th>
<th>Serum Creatinine</th>
<th>Clinical Description</th>
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| Grade 1   | < 1.6 mg/dL < 140 μmol/L | Non Azotemic AKI:  
a. Documented AKI: Historical, clinical, laboratory, or imaging evidence of acute kidney injury, clinical oliguria/anuria, volume responsiveness**, and/or  
b. Progressive non azotemic increase in blood creatinine; ≥ 0.3 mg/dl (≥ 26.4 μmol/L) within 48 hours  
c. Measured oliguria (< 1 ml/kg/hr) or anuria over 6 hours |
| Grade 2   | 1.7 – 2.5 mg/dl 141 – 220 μmol/L | Mild AKI:  
a. Documented AKI and static or progressive azotemia  
b. Progressive azotemic increase in blood creatinine; ≥ 0.3 mg/dl (≥ 26.4 μmol/L) within 48 hours, or volume responsiveness**  
c. Measured oliguria (< 1 ml/kg/hr) or anuria over 6 hours |
| Grade 3   | 2.6 – 5.0 mg/dl 221 – 439 μmol/L |  |
| Grade 4   | 5.1 – 10.0 mg/dl 440-880 μmol/L | Moderate to Severe AKI:  
a. Documented AKI and increasing severities of azotemia and functional renal failure |
| Grade 5   | > 10.0 mg/dl > 880 μmol/L |  |

** Volume responsive is an increase in urine production to > 1 ml/kg/hr over 6 hours; and/or decrease in serum creatinine to baseline over 48 hours

Table 2. Causes for AKI in cats
Renal ischemia (hypoperfusion)

Dehydration Shock  
Trauma Hemorrhage  
Anesthesia Surgery  
Sepsis Burns  
Hyperthermia Hypothermia  
Hemolysis Myoglobinuria  
ACE Inhibitors Non-Steroidal Anti-Inflammatory Drugs (NSAID)

**Note that renal ischemia can occur in the absence of systemic arterial hypotension.

Nephrotoxins
More common

- Glycols (Ethylene Glycol)
- Antimicrobials  
  o Aminoglycosides  
  o Amphotericin-B  
  o Sulfonamides - dehydration  
  o Tetracyclines – IV  
  o Fosfomycin – not dogs  
- Easter Lilly – Cats

Less common

- Hypercalcemia  
  o Cholecalciferol Rodenticide  
  o Cholecalciferol – Diet  
  o Calcipotriene – antipsoriasis cream
- Cancer Chemotherapeutics  
  o Platinum compounds alone and more so when combined with piroxicam
Radiocontrast Agents - IV
Heavy Metals

Miscellaneous causes of AKI
- Renal thromboembolism – renal infarction
- Acute-on-chronic renal failure
- Renal amyloidosis with acute papillary necrosis

Acute hyperphosphatemia
- Tumor lysis syndrome
  - Phosphate enema
  - Phosphate acidifier
  - Massive soft tissue trauma
- Pancreatitis
- Food-associated renal failure – FARF
  - (melamine with cyanuric acid tainting)

References
The incidence of the diagnosis of CKD in cats is said to be two to three times as frequently compared to dogs and is especially common in geriatric cats. CKD is clinically characterized by the development of variably progressive irreversible intrarenal lesions and loss of renal functions. Compensatory increases (so called adaptations) in glomerular hemodynamics and glomerular volume may actually be maladaptive in the long term as they cause increased protein trafficking across the glomerulus.

The initial diagnosis of CKD is made on a combination of findings from clinical signs, physical examination (especially large or small kidneys, irregular kidneys), renal imaging, urinalysis, and serum biochemistry. A surprising number of cats with CKD have upper urinary tract uroliths at the time of initial diagnosis. Abdominal radiographs should be routinely obtained to determine the presence or absence of radiopaque stones. Renal and ureteral ultrasonography should be performed in all cats in which renal or ureteral stones were found on radiography in order to tell whether or not there is an obstructive component to the CKD. T4 should be measured in all cats with suspected CKD since hyperthyroidism can mask the detection of azotemia by its effects that increase GFR and RBF; hyperthyroidism may also contribute to progression of CKD through a variety of mechanisms including intraglomerular and systemic hypertension. Conventional wisdom and experience suggests that client-owned cats with healthy kidneys elaborate urine with a specific gravity of >1.035. This concept was recently validated in a study of cats evaluated at first opinion clinics. Cats with USG < 1.035 should undergo further diagnostic investigation to determine if they have an endocrine or renal disorder with or without associated clinical signs. A surprising number of experimental 7 and clinical cats with CKD continue to be able to elaborate urine with a USG >1.035, so the presence of “concentrated” urine and mild to moderate azotemia does NOT exclude the presence of primary kidney disease in cats as it often does in dogs. Cats that have thin body condition, prior periodontal disease or cystitis, anesthesia or documented dehydration in the preceding year, or being a neutered male (vs spayed female) were reported to be at increased risk for the diagnosis of CKD.

A staging system initially based on the level of serum creatinine concentration has been developed by IRIS (International Renal Interest Society) for use in cats that are hydrated and stable. Serum creatinine is measured again on at least 2 occasions 2 weeks apart by the same lab. Sub-staging is then based on the degree of proteinuria as measured by UPC and also the magnitude of blood pressure. Staging using this system is designed to detect CKD much earlier than with traditional methods and also to potentially match treatments by stage. Normal and stage 1 CKD cats have serum creatinine concentrations < 1.6 mg/dl (< 140 μmol/L). Normal cats usually have a UPC < 0.2, with 0.2-0.4 considered borderline increased, and > 0.4 overtly proteinuric. Details of this staging system can be found online at http://www.iris-kidney.com. This staging system does not indicate the underlying cause for the CKD which requires other diagnostic workup to determine. It is important to remember that nearly all studies on the effect of diet or drugs have studied overtly azotemic cats (serum creatinine > 2.0 mg/dl). It has not been determined whether or not the salutary effects of treatment in azotemic cats confer the same benefits to CKD cats at earlier stages.

Tubulo-interstitial nephritis of unknown origin is the most common cause of azotemic CKD in the cat, as in the dog. However, cats have several renal diseases that deserve additional consideration as compared to dogs including breed related predilection for renal amyloidosis (Abyssinian, Oriental Short Hair) and polycystic kidney disease (Persian, Himalayan). Cats have greater frequency of CKD associated with renal LSA than dogs. Peri-nephric pseudocyst can be associated with CKD in cats and should be considered as a differential diagnosis for apparent renal enlargement in addition to renal LSA and hydronephrosis.

A variety of interventions (diet and drugs) can slow the progression of the renal disease, improve the quality of life for the patient, and/or extend the quantity of life. Dennis-I just moved this here as it opens your discussion re treatment.

**Dietary interventions for CKD**

Dietary therapy remains the cornerstone of management of CKD. Diet modifications include phosphorus restriction (most important), providing reduced quantity but high quality protein, adequate non protein calories from fat and CHO’s, modifying sodium content (not the degree of restriction once recommended by some), supplementing potassium, B vitamins, alkali as needed and providing omega three fatty acids. In one 2-year study, cats with a serum creatinine > 2 mg/dl fed a renal diet had a median survival time that was 2.4 times longer than cats fed a maintenance diet (633 days vs 264 days). In another study, IRIS stage 2 & 3 cats were followed for 24 months. Cats fed the maintenance diet had more uremic episodes and more renal-related deaths compared with cats fed the renal diet. In a study of 175 CKD cats fed 1 of 7 different renal diets, the median survival time was 16 months (12 to 23 months) compared to a median survival time of 7 months for cats eating their maintenance diet. Interestingly, the longest survival period was found in cats eating a renal diet with the highest eicosapentaenoic acid (diet not available in North America), otherwise the renal diets were similar...
in composition. 10 Patients are more likely to accept a new renal diet if offered before uremia develops and a gradual transition may be needed.

The number one reason to restrict dietary protein is to provide an adequate degree of restricted intake of phosphorus, especially those associated with animal tissues in the diet. Decreased production of nitrogenous wastes can occur in those with large increases in BUN, and consequently improve the clinical well-being of the pet even though renal function remains unchanged. If proteinuria is present, dietary protein restriction may lower the magnitude of proteinuria through obscure mechanisms. Reduced dietary protein intake may also lessen inflammatory, fibrogenic and oxidative stress pathway.11 The amount to restrict dietary protein is not known, so it is currently recommended to provide at least maintenance levels. For cats with CKD, the minimum dietary protein requirement suggested is 20% of calories, which equates to 24% protein on a dry-matter basis.11-13 Others suggest 28–35% (DMB).15 It is emphasized that less total dietary protein can be fed if high biologic value proteins, such as egg, are fed.13 Lowering animal-derived protein (source of phosphates) in the diet may be essential to lower dietary phosphorus intake needed to achieve target levels of serum phosphorus.16 Too much dietary protein restriction can and often does result in protein: calorie malnutrition. Protein malnutrition from any cause is strongly correlated with morbidity and mortality. If protein malnutrition becomes evident in a patient (hypoalbuminemia, anemia, weight loss or loss of lean muscle mass), then the amount of protein should be increased until signs are no longer evident. Cats with sarcopenia, regardless of the stage of renal disease, may require more protein than a renal diet can provide-careful monitoring and adjustment will be needed in these cats.

Pets with CKD often suffer from poor appetite that can contribute to poor body condition. This is often associated with decreased prognosis as the owner’s often euthanize when quality of life is perceived as unacceptable. Mirtazapine (Remeron) helps not only with appetite but with uremic-associated nausea. Recent work in cats indicates mirtazapine can be administered at a low dose (1.88 mg) every 48 hours to cats with CKD, but was only studied for its effects for 3 weeks.17,18 Remember that mirtazapine and cyproheptadine cannot be administered concurrently. Cyproheptadine is in fact used as an antidote for serotonin effects of mirtazapine overdose. Maropitant (Cerenia): NK-1 receptors are in the chemoreceptor trigger zone, in the emetic center itself, as well as peripherally. Consequently, Cerenia is a great choice to treat vomiting/nausea in renal cats. Despite the label recommendation, many specialists are recommending Cerenia for longer than 5 days (personal communication with specialists and with Zoetis scientists). Dose: 1 mg/kg PO once daily. Refrigerate to help alleviate the sting associated with injectable cerenia.19 Omeprazole (Losec): Studies in cats have also shown Omeprazole to be more effective than H2 blockers such as famotidine and ranitidine in decreasing gastric acidity.20 Dosage: 0.5-1 mg/kg once a day. If H2 blockers are used, dosages recommended are Famotidine (Pepcid®) 0.5 mg/kg IM, SQ, PO q 12 hours or Ranitidine (Zantac®) 1-2 mg/kg q 12 hours (cat). Studies have shown most cats with uremia do have elevated gastrin levels (and likely corresponding hyperacidity) but no GI ulcers.20,21 Consequently, sucral fate is not usually indicated. The GI bleed with uremia could be from dysregulation of the vasculature and platelet dysfunction associated with uremia.20,21 If used, a dose of 0.25-0.5 g/cat q 12 hours is recommended. In some countries sucral fate is used as an intestinal phosphate binder due to its aluminum content. Ondansetron at the time of this writing is not highly recommended. The bioavailability is not high (maybe 30% at best in cats) and the half-life is very short (it would be best to give this drug 4 times/day).22

Phosphorus
Higher concentrations of serum phosphorus predicted an increase in serum creatinine > 25% above baseline over 12 months in 47% of CKD cats.23 Serum phosphorus was the only clinicopathologic variable predictive of survival in one study of CKD cats. There was an increase in risk of death of nearly 12% for each mg/dl increase in phosphorus in the same study.24 Higher phosphorus concentration was associated with a higher risk of death within 1 month in another study.25 Even when serum phosphorus was within the reference range, cats with CKD of one study that had phosphorus concentration > 4.7 mg/dl serum phosphorus had a higher risk of death compared to CKD cats in which circulating phosphorus concentration was ≤ 4.7 mg/dl.26

Dietary phosphorus restriction is critical at least from Stage 2 onwards; there is no data to evaluate any potential benefit of Pi restriction in Stage 1. Compared to the average grocery or pet store foods, the renal friendly veterinary diets are restricted in phosphorus by 70 to 80%. Serum phosphorus concentration may increase in CKD pets that increase their food intake following other supportive CKD treatments. Renal diets may provide sufficient dietary phosphate restriction during early stages of CKD but often the addition of dietary phosphate binders will be needed to reach targeted control of serum phosphorus. Early phosphorus restriction in CRF has been shown in dogs and cats to blunt or reverse renal secondary hyperparathyroidism.27

Intestinal phosphate binders
Aluminum salts are the most widely used phosphate binders in cats. Aluminum based phosphate binding agents (aluminum hydroxide, aluminum carbonate) are highly effective in lowering serum phosphate levels, forming insoluble and nonabsorbable aluminum phosphate precipitates in the intestinal lumen. THERE IS NO KNOWN SAFE DOSE OF ALUMINUM SALTS FOR HUMANS WITH CKD. Detrimental effects of aluminum based phosphate binders as described in humans seen in humans have not been systematically evaluated in small animal patients and are rarely clinically appreciated. As cats with CKD can live for years on
treatment, concerns for aluminum accumulation deserve more study as to long-term safety. Calcium-based binders are not as effective as aluminum salts, having a lower affinity for phosphorous, thus effective binding of dietary phosphorous requires large doses of calcium, often enough to induce hypercalcemia in humans. The most commonly used calcium based phosphate binders are calcium carbonate and calcium acetate. Animals should be monitored for development of hypercalcemia whenever calcium-containing phosphorus binders are used. Sevelamer hydrochloride (Renagel®, Genzyme Corporation) and the more recently FDA approved Sevelamer carbonate (Renvela®, Genzyme Corporation) are organic polymers that do not contain aluminum or calcium and are not absorbed from the gastrointestinal tract (excreted entirely in feces). Their effects on dogs and cats with clinical CRF have not been reported. Epakitin® (Vetoquinol Inc.) is marketed as a complementary feed on the veterinary market. It contains the adsorbent chitosan (8% crab and shrimp shell extract), 10% calcium carbonate, and 82% lactose and is designed to reduce GI phosphorus absorption and to lower urea nitrogen due to effects of reduced protein digestibility. The results of two studies suggest that this supplement could be an alternative to prescription of renal veterinary diets thereby allowing some cats to continue on their regular diets while still reducing the risks for progression of CKD associated with total body phosphorus burden. We have, however, observed the development of hypercalcemia in a few CKD cats with the use of this product probably as a consequence of the calcium carbonate. Lanthanum carbonate (Fosrenol®, Shire Pharmaceuticals) is a non-aluminum and non-calcium containing intestinal phosphate binder and is indicated for use in human patients with end-stage renal failure to reduce serum phosphorous. Very little lanthanum is absorbed across GI tract and lanthanum accumulates to a far less degree following absorption compared to aluminum since lanthanum undergoes extensive hepatic excretion whereas aluminum is excreted mostly by the kidneys. Lanthanum appears to have minimal toxicity in humans. A recent abstract in a small number of CKD cats administered lanthanum carbonate in food at 95 mg/kg/day to achieve very modest serum phosphate control. Several reports of the efficacy and safety of lanthanum carbonate treatment in cats have been published. Lanthanum carbonate octahydrate (Lantharenol® Bayer HealthCare AG) is marketed as a feed additive for adult cats in order to decrease intestinal phosphate absorption. Renalzin® (Bayer HealthCare AG) is the proprietary name for the delivery system of Lantharenol® and comes as a pump system that delivers lanthanum carbonate along with kaolin and vitamin E at appropriate doses to food for cats. This system is widely available in the UK and Europe, but not in the USA or Canada. The proprietary formulation of human lanthanum carbonate is soon to become available as a generic product.

Pronefra® recently has been launched (Virbac, France) as a dietary supplement for cats with CKD. This product provides a combination of calcium and magnesium carbonate as the intestinal phosphate binders, chitosan for “uremic toxin” binding, vasoactive peptides (designed to maintain normal blood pressure) and an extract of Astragalus membranaceus (Chinese herb for anti-inflammatory and anti-fibrotic effects). Safety of this product was reported in 10 normal cats in which Pronefra was added to the food once daily for 12 weeks. No changes in circulating calcium or magnesium were noted at during this study. Presently there are no reported studies of safety or efficacy in clinical cats with CKD treated with this supplement.

Novartis has developed a new oral phosphate binder for cats called Lenziaren ® (SBR759). Iron oxide with starch and sucrose exist in this preparation as an insoluble complex. A dose of 0.5 to 1.0 Gm/cat/day is recommended when added to standard diets. A dose of 0.25 Gm/cat/day to 1.0 Gm/cat/day is recommended when adding this phosphate binder to a renal diet. Safety and efficacy of Lenziaren® in cats with CKD are not yet reported. Lenziaren is touted by the authors as a phosphate binder that does not contain aluminum, calcium, or lanthanum that could be problematic in cats with CKD. That is true for the aluminum and calcium as a factor in favor of its use, but there is no known toxicity of lanthanum yet reported.

### Control of proteinuria

Cats with azotemic CKD increased their risk for death or euthanasia when the UPC was 0.2 to 0.4 compared to <0.2 and was further increased in cats with UPC of >0.4. The prognosis for survival is influenced by the UPC despite what has traditionally been thought to be low-level proteinuria. The effect of treatments that lower proteinuria on survival have not been specifically studied. Since even low-level proteinuria is a risk factor for cats to not survive, it is prudent to consider treatments that lower the amount of proteinuria in those with CKD. See discussions about the potential benefits of dietary protein restriction (above) and RAAS inactivation (below) to reduce the magnitude of proteinuria.

### RAAS inactivation

RAAS inactivation results in decreased generation of angiotensin-2 and aldosterone that can exert benefits to reduce progression of CKD. These beneficial effects can occur through variable combinations of reduction in systolic blood pressure, decreased intraglomerular hypertension, decreased glomerular proteinuria, and less generation of pro-inflammatory and pro-fibrotic cytokines in patients with CKD.

Benazepril is labeled for treatment of azotemic CKD in cats in the UK, Europe, and Canada (Fortekor®), but not in the USA. The ACE-inhibitor benazepril consistently reduces proteinuria in various stages of CKD in cats even when the base line level of proteinuria is seemingly trivial. Benazepril has been shown in two clinical studies to reduce the UPC in cats with azotemic CKD.
Despite reduction in proteinuria in CKD cats with initial UPC > 1.0 that were treated with benazepril in one study, increased survival time was not found over placebo. The average survival time of all benazepril treated cats in this study was 501 days vs. 391 days for placebo treated cats but this effect did achieve statistical significance. In another study of 61 cats with CKD, benazepril treatment for 189 days appeared to stabilize those in IRIS stage 2 or 3 with less transition to stage 4 compared to treatment with placebo, though this effect did not achieve statistical significance (low number of cats and short duration of study).

The angiotensin receptor blocker (ARB) telmisartan (Semintra® Boehringer Ingelheim) was approved by the European Commission in 2013 for use in the European Union as a drug for use in cats with CKD and is available for use in Canada but not yet in the USA. Semintra was found to be at least as effective as benazepril in reducing proteinuria in cats with CKD and was well tolerated. A US Patent application was filed in July 2013 by Boehringer Ingelheim. It is not clear when or if an ARB should be chosen to reduce RAAS activity instead of an ACE-Inhibitor for treatment of CKD in veterinary patients to reduce proteinuria, systemic blood pressure, or intra-renal inflammation. A veterinary review of the RAAS system, ACE-Inhibitors and ARB’s provides more detail for the interested reader.

**Activated vitamin-D metabolites: calcitriol**

Calcitriol treatments help to decrease PTH or prevent its increase in those with renal secondary hyperparathyroidism. This occurs largely through genomic effects to block PTH synthesis in addition to a mild calcemic effect, and anti-proliferative effect that prevents parathyroid gland hyperplasia. It has become increasingly apparent that calcitriol has major beneficial anti-inflammatory and anti-fibrotic intrarenal effects that are independent of effects on PTH. During treatment of CRF patients with calcitriol, simultaneous monitoring of serum ionized calcium, serum phosphorus and PTH concentrations is the ideal way to document successful and safe control of renal secondary hyperparathyroidism. Calcitriol should not be administered until hyperphosphatemia has been controlled. If the Ca X P solubility product exceeds 60-70, calcitriol should be avoided because of the risk of soft-tissue mineralization.

In a recent study of dogs with azotemic CKD that were treated with calcitriol a median of 365 days survival was observed compared to 250 days in dogs treated with placebo (renal diet in both groups). Similar studies were performed in cats by the same investigators who concluded that there is no advantage to calcitriol treatments in cats with CRF but the study followed cats for just one year. In order to show a difference in treatment effect, if one exists, studies in cats with CKD must be conducted for at least 2 and possibly 3 years due to the inherently slow nature of the progression of chronic renal disease in this species. The authors believe that beneficial effects of calcitriol treatment are likely to occur in cats with CKD.

A compounding pharmacy will be needed to reformulate calcitriol from the human parent drug to a concentration suitable for the dosing of cats. We recommend intermittent rather than daily dosing treatment protocols as the standard of care since less hypercalcemia occurs using this protocol. The equivalent dose given at 2.5 mg/kg daily is given instead every 3.5 days. This works out to a dose of 9 ng/kg (8.75 ng/kg rounded to 9 ng/kg). It is important to give the dose every 3.5 days, rather than on day 1 & 4. For example if a dose is given Tuesday PM the next dose should be given Saturday AM. This is the longest time in between dosing that will still suppress the parathyroid gland. This method of dosing is especially attractive for cat owners since medication will only be given twice weekly.

**Systemic hypertension**

Systemic hypertension is common in cats with CKD with 13-28% of cats presenting with hypertension when CKD is first diagnosed and up to 65% of cats developing hypertension at some point during the progression of their renal disease. Cats that have systemic hypertension from a variety of causes have been shown to survive longest when their blood pressure is well controlled.

Enalapril or benazepril as monotherapy has not been very effective for treatment of hypertensive cats or dogs. The calcium channel blocker, amlodipine has been used successfully in cats at a dosage 0.625 to 1.25 mg per cat given orally once per day. Follow-up evaluations should be scheduled for one week after beginning treatment with amlodipine. Adverse effects (including hypotension) are very uncommon with the use of amlodipine in cats.

**References**


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How common is hypercalcemia in cats?
The frequency of the detection of hypercalcemia in cats has dramatically increased in many regions of the world over the past 20 years mostly due to the diagnosis of idiopathic hypercalcemia (IHC).\textsuperscript{1,2} Hypercalcemia is most often initially defined in primary care practice by the finding of increased serum total calcium on routine serum biochemistry. Mild hypercalcemia based on serum total calcium is often overlooked during analysis of serum biochemical profiles, so the frequency of hypercalcemia is likely to be more common than generally recognized. Mild serum total hypercalcemia is frequently attributed to hemoconcentration from dehydration.\textsuperscript{8}

Total serum calcium cannot be reliably used to predict the metabolically active ionized calcium fraction in cats.\textsuperscript{8} There was an overall diagnostic discordance of 40\% during evaluation of 434 feline serum samples using total calcium to predict ionized calcium in cats of one study. Ionized hypercalcemia and normocalcemia were underestimated and ionized hypocalcemia was overestimated.

Characterization of hypercalcemia
Once ionized hypercalcemia has been identified, the next step is to determine if the process is PTH-dependent (high PTH from failure to suppress abnormal parathyroid glands) or PTH-independent (PTH is appropriately suppressed as the response of normal parathyroid glands). In a study of 322 cats, ionized hypercalcemia was parathyroid independent in 82\%, equivocal in 10\%, and parathyroid-dependent in 8\% of these cats.\textsuperscript{9} In cats with parathyroid-independent hypercalcemia, malignancy-associated hypercalcemia (MAH) needs to be excluded. MAH most often results from humoral mechanisms as the tumor secretes calcemic substances such as PTHrP into the circulation; local osteolytic hypercalcemia is far less common. When PTHrP is reported to be high, the presence of malignancy is likely. A low or undetectable PTHrP does not exclude malignancy as the cause for hypercalcemia since other cytokines that cause calcemia can be elaborated by the tumor instead of PTHrP on occasion.

If the diagnostic evaluation does not reveal malignancy as the cause for parathyroid-independent hypercalcemia (PTHrP and body cavity imaging), evaluation of circulating vitamin D metabolites may be useful in determining the underlying cause or mechanism for the hypercalcemia. Hypervitaminosis D is classically characterized by increased concentrations of circulating 25(OH)-vitamin D (calcidiol) following excess ergo/cholecalfierol exposure from food\textsuperscript{10,11} or from cholecalciferol-containing rat-bait.\textsuperscript{12,13} Increased circulating calcitriol has been reported in cats with granulomatous disease and hypercalcemia, likely the result of unregulated conversion of calcidiol to calcitriol by activated macrophages.\textsuperscript{14-16}

What are the causes of hypercalcemia in cats?
The frequency for the occurrence of total serum hypercalcemia from biochemical panels from sick or well cats is not known. The only large survey of the causes of hypercalcemia in cats was reported from a veterinary teaching hospital based on the measurement of serum total calcium in 2000.\textsuperscript{17} Ionized hypercalcemia concentration has been sporadically reported in cats with specific diseases, but not in a series of cats with varying causes of hypercalcemia. Idiopathic hypercalcemia, CKD, and neoplasia are the most common and important differential diagnoses to exclude as the cause for parathyroid independent hypercalcemia. Overt hypervitaminosis D, granulomatous disease, and hypoadrenocorticism are other far less common causes of hypercalcemia in cats. Calcium oxalate urolithiasis was reported to be associated with hypercalcemia in cats; however, it is likely that hypercalcemia preceded the formation of stones rather than the urolithiasis acting as a stimulus for the formation of hypercalcemia.\textsuperscript{17,18} IHC was not considered as a diagnostic category in one large study of cats with hypercalcemia,\textsuperscript{17} but in another study the occurrence of IHC in 20 cats was published that same year.\textsuperscript{18} Primary hyperparathyroidism was infrequently diagnosed as the cause of the hypercalcemia at a teaching hospital (4 of 71 cats),\textsuperscript{17} but this diagnosis is far more frequently made by veterinary endocrine referral laboratories.\textsuperscript{19} Based on the number of consultations by veterinary internists and endocrinologists, as well as sample submissions to endocrine laboratories, idiopathic hypercalcemia (IHC) is currently the most-common cause of hypercalcemia in cats in North America and likely so in other parts of the world.\textsuperscript{1,2,5-7}

While MAH is the number one cause of pathological hypercalcemia in the dog,\textsuperscript{19} it occurs far less frequently in the cat. Based on serum total calcium and how the data is parsed, MAH is 3rd in frequency behind IHC and CKD in cats with hypercalcemia.\textsuperscript{17} In dogs, the overwhelming cause of MAH is lymphoma with occasional carcinoma as the diagnosis,\textsuperscript{19} whereas in cats lymphoma and carcinomas each account for about 1/3 of the cases.\textsuperscript{17} Patients with MAH are usually “sick” as it takes a reasonably large tumor burden to synthesize the messengers that result in hypercalcemia.
In a report from 427 cats with IHC evaluated at an endocrinology laboratory, the age at diagnosis ranged from 0.5 to 20 years (mean 9.8 ± 4.6 yr). Males and females were equally represented in this study. Long-haired cats were noted to be overrepresented at 27% of the cases in this report, but not in a recent case-control epidemiological study (data analyzed post Todd Green Master’s Ohio State University 2008).

No clinical signs were noted in 46% of IHC cats. Other clinical signs were largely related to gastrointestinal signs, including mild weight loss (18%), chronic constipation (5%), vomiting and decreased appetite. IBD was diagnosed in 6% of the IHC cats of this study. Lower urinary tract signs may be observed, especially if urolithiasis is present. Uroliths or renoliths were observed in 15%, and calcium oxalate stones were specifically noted in 10% of cases. Polyuria/polydipsia has not been frequently reported in cats with IHC.

In many instances, hypercalcemia based on measurement of total serum calcium is fortuitously discovered following submission of serum samples from wellness examinations, pre-anesthetic evaluation of seemingly healthy individuals, those with routine medical conditions, and those from cats forming calcium-oxalate stones. Hypercalcemia is also sometimes discovered following submission of samples from cats with seemingly trivial clinical complaints like intermittent vomiting of hairballs. Though many cats with IHC do not have obvious clinical signs at first look, a more careful review of the history and physical examination often discloses some abnormality that could be explained by persistence of chronic ionized hypercalcemia. This includes low-grade weight loss, loss of muscle mass, and lethargy. Intermittent vomiting and constipation are also possibly due to adverse effects of ionized hypercalcemia on gut motility. Chronic ionized hypercalcemia is a risk factor for the genesis of calcium oxalate urolithiasis and for the development of chronic renal injury resulting in CKD that may take months to years to develop.

How is the diagnosis of IHC established?
The diagnosis of IHC is one of exclusion after initially confirming that the ionized calcium is increased. All the known causes of hypercalcemia should ideally be eliminated – this kind of workup can be exhaustive and expensive. The increase in circulating ionized calcium in IHC can be mild, moderate, or severe, as it can also be with other causes of hypercalcemia. Often mild increases in total or ionized calcium that are discovered fortuitously tend to increase over time, but to a varying magnitude. We have observed the ionized calcium concentration to fluctuate into and above the reference range, especially when the hypercalcemia is marginal in magnitude. We have observed large fluctuations in total and ionized calcium concentrations on occasion in some cats with IHC and those with primary hyperparathyroidism.

In order to exclude other causes of hypercalcemia, a minimum database including a CBC, biochemistry profile and urinalysis, should be performed. Additionally, analysis of PTH and 25-hydroxyvitamin D are necessary to rule out hyperparathyroidism and hypervitaminosis D as the cause of the hypercalcemia. The typical pattern for calcium regulatory hormones in IHC would be for the PTH concentration to be within the reference range (often lower end), the PTHrP concentration to be undetectable, and to have a normal serum ionized magnesium concentration. Most 25-hydroxyvitamin D and calcitriol concentrations are usually within the reference range, but a few cats with IHC have been noted to have values increased above the reference range.

Chest radiographs are useful to rule out metastatic pulmonary nodules and mediastinal lymphoma that may be associated with hypercalcemia. Unlike in dogs, mediastinal lymphoma is not common in cats. A combination of abdominal radiographs and ultrasonography can be useful to determine the presence of urolithiasis (kidney, ureter, bladder, urethra), obstructive nephropathy from the stones, or the presence of inflammatory/infiltratitve masses that could be associated with the genesis of the hypercalcemia. Treatment recommendations and prognosis may change with the presence of stones and their location.

Should all cats with IHC receive treatment?
Cats with minimal increases in circulating calcium concentrations are often ignored in clinical practice since many of these cats have mild or no apparent clinical signs. Even though obvious clinical signs are often not apparent, subtle clinical signs often exist. Excess calcium can be toxic to cells, exerting either physiological or structural effects particularly in the central nervous system, gastrointestinal tract, heart, and kidneys. Mineralization of soft tissues is an important potential complication related to the presence of ionized hypercalcemia that is in part determined by the concomitant concentration of serum phosphorus, but this does not develop in all IHC cats. The clinical outcome for cats with IHC that have not been treated has not been established following the initial diagnosis. An argument can be made to withhold treatment when an IHC cat has no recognizable signs, no identified risk factors for urolithiasis or CKD, and the increase in ionized calcium is minimal. A stronger argument can be made to treat IHC cats in which the ionized calcium concentration continues to escalate. The strongest argument to start treatment exists for cats that have ongoing weight loss, depression, vomiting, constipation, urinary stones, emergence of CKD and or development of sub-maximally concentrated urine.
Treatment of IHC – diet
Management of IHC usually begins with a dietary recommendation to attempt to restore normocalcemia. Reports of treatment outcome following dietary change are quite limited, so diet recommendations are largely based on expert opinion and uncontrolled case studies in small numbers of cats. We have observed decreased circulating ionized calcium in some cats following dietary change, but the magnitude and duration of this decrement can be quite variable. Future studies comparing test and control diets are needed to determine the effects, if any, of altering intake of nutrient(s) on concentrations of the calcium regulatory hormones PTH, calcidiol, calcitriol, and 24,25(OH)2-vitamin D in addition to that for ionized calcium.

Is there one specific dietary nutrient on which we should focus that will consistently decrease circulating ionized calcium?
Regulation of the circulating calcium concentration is dynamic and complex. It has not been determined how much of the hypercalcemia in IHC cats results from too much dietary calcium intestinal absorption, increased bone resorption, reduced renal excretion of calcium, or combinations of these processes. Many of the nutrients in the diet interact with each in ways that affect dietary calcium absorption and not all calcium in the diet is biologically available for absorption. Vitamin D is one obvious dietary nutrient that can affect intestinal absorption of calcium and it also has effects on osteoclastic bone resorption that can contribute to the degree of calcemia. Vitamin A has effects on the osteoclast that can work in concert with vitamin D to increase bone resorption.

What do we know about dietary calcium content in the management of IHC?
Some veterinary nutritionists recommend diets to treat IHC based on a decreased calcium content on a g calcium/100 kcal (Mcal) energy basis. Minimal and maximal nutrient recommendations for cat food are provided by the Association of American Feed Control Officials (AAFCO) and the National Research Council (NRC). Most diets sold over-the-counter should meet AAFCO requirements; however, veterinary therapeutic diets may be specifically modified in order to provide certain nutrients at concentrations less than AAFCO minimums. The average calcium content of grocery store foods in the USA is approximately 2.0 to 3.0 g calcium per Mcal (200-300 mg/100 kcal), though some contain up to 6.0 g calcium per Mcal (600 mg per 100 kcal). Some of the highest calcium diets are “high-fiber” diets; thus one must carefully weigh the pros and cons of recommending a high-fiber diet for dietary management of IHC when there is some evidence that reducing dietary calcium may be effective in restoring normocalcemia. Nutrient concentrations of diets can be found either in product guides or by contacting the diet manufacturer, but this information is not readily available from the routine diet label. Nutrient profiles are constantly evolving and this information may change up to every 6-12 months. For feline adult maintenance, the NRC recommended allowance (RA) is 0.72 g calcium per Mcal and the AAFCO minimum is 1.5 g calcium per Mcal.

Feeding of a high protein and low carbohydrate food similar to what cats would eat in the wild (i.e., 40-60% of calories from protein; 30-50% of calories from fat, and <15% of calories from carbohydrates) has been recommended to effectively lower serum calcium concentration in some cats with IHC, especially those with low magnitude hypercalcemia. This nutrient profile is what would be expected from veterinary therapeutic diets designed for cats with diabetes mellitus and also many over-the-counter canned feline diets. In reviewing these types of diets however, it should be noted that calcium content varies from about 1.5 to 5.5 g per Mcal.

What do we know about dietary vitamin D content in the management of IHC?
IHC is not the result of obvious excess dietary vitamin D intake since serum concentrations of 25(OH)-vitamin D have been within the reference range in most cats with IHC. However, the minimal requirement for vitamin D in cats is debatable since reference ranges have been established in cats fed vitamin D-supplemented diets. Normal concentrations of 25(OH)-vitamin D could still potentially be associated with IHC in cats if there are up-regulating mutations in the VDR (vitamin D receptor). These possibilities have not yet been investigated.

For adult cats, the NRC-RA for dietary vitamin D3 (cholecalciferol) is 70 IU per Mcal. The safe upper limit (SUL) is listed as 7,520 IU per Mcal. AAFCO minimum and maximum recommendations for feline adult maintenance are 125 and 2,500 IU per Mcal, respectively. Clearly, there is a wide range of acceptable dietary vitamin D in commercial cat foods. Feeding a diet formulated to be low in vitamin D content at < 200 IU per Mcal has been recommended in dietary treatment of cats with IHC.

How helpful are high fiber diets in restoration of normocalcemia in cats with IHC?
Higher fiber diets were associated with the restoration of normocalcemia in 5 of 5 cats with calcium oxalate stones and a likely diagnosis of IHC (high ionized calcium concentration) in one report. The effects of fiber on intestinal absorption of calcium are complex and depend on the type and amount of fiber in the diet and the interactions with other nutrients in the diet. It has been theorized that supplemental fiber may lead to increased binding of intestinal calcium, preventing its absorption, and also to decreased intestinal transit time through the small intestine, reducing calcium absorption. The salutary effect of a higher fiber diet, if any, is not simply due to the binding of calcium to fiber. It appears to be common practice for most manufacturers to increase the concentration of calcium in high-fiber diets to offset the potential for decreased absorption.

How helpful are higher salt diets in management of IHC?
Treatment with higher salt content diets has not been studied in IHC cats, with or without calcium oxalate stones. Higher salt intake potentially could promote increased water intake, volume expansion, and a dilution effect that would decrease circulating ionized calcium to some degree. Increased water turnover would then create more dilute urine that should help prevent calcium oxalate stone
growth by reducing RSS. Increasing salt intake up to 3.7 g per Mcal has been reported to be safe without detection of deleterious effects on renal function, cardiovascular function, and systemic blood pressure when studied in normal cats, geriatric cats, and cats with surgically reduced renal mass.31-35 Future studies of higher dietary salt intake for treatment of cats with IHC are warranted.

**Treatment of IHC- glucocorticosteroids and oral alendronate**

We do not recommend starting drug therapy immediately after the diagnosis of IHC since dietary treatment is effective in restoration of normocalcemia in some cats. Treatment with glucocorticoids restores normocalcemia or dramatically reduces the ionized calcium concentration in most cats with IHC, at least initially. A maximal decline in calcium to within the reference range often requires dose escalation and the beneficial effect may be transient. Approximately 80% of cats with IHC become normocalcemic with 1.5 to 2.0 mg/kg/day prednisone per day, but some may require increasing doses to remain normocalcemic over time.36 It is important to not prescribe glucocorticosteroids before the diagnosis of the hypercalcemia has been established with some certainty, otherwise cytolytic effects in LSA and myeloproliferative disorders will make definitive diagnosis difficult or impossible. A mild calcium-lowering effect can be exerted by use of glucocorticosteroids in other forms of malignancy-associated hypercalcemia and in those with primary hyperparathyroidism. It is also preferred to have biopsy-proven IBD before the start of glucocorticosteroids. Oral prednisolone achieves greater maximal concentration in the circulation than does oral prednisone in the cat, possibly due to greater GI absorption of prednisolone or less hepatic conversion of prednisone to prednisolone.37 Prednisolone is given orally at 5 – 10 mg/cat/day for 1 month before reevaluation. Though prednisolone can be effective in restoration of normocalcemia in IHC cats, we now usually consider prednisolone as treatment after oral bisphosphonate treatment has failed to restore normocalcemia. In these instances, prednisolone is prescribed in addition to the oral bisphosphonate, but much lower doses of prednisolone may now be effective during combination drug therapy. Long-term treatment with prednisolone contributes to muscle wasting4,6 and possible induction of diabetes mellitus in some cats.

**Bisphosphonate treatment for IHC cats**

Historically, oral bisphosphonates have been recommended to treat IHC cats when dietary modification and prednisolone treatment have been unsuccessful in restoration of normocalcemia. Oral alendronate has become our preferred option to treat IHC cats after dietary modification has failed to restore normocalcemia.28 Even though not extensively reported, we now consider bisphosphonate therapy a safer alternative to glucocorticosteroid use in cats that failed dietary intervention. Treatment with bisphosphonates may be useful to decrease the magnitude of hypercalcemia in cats with IHC by altering osteoclastic bone resorption. IV treatment with bisphosphonates is almost never needed in IHC since the hypercalcemia is chronic and the cats are usually not in an acute crisis.

The long-term safety and efficacy of oral alendronate therapy has not been reported in cats. The safety and efficacy of oral alendronate treatment given once weekly for 6 months was reported in 12 cats with IHC.38 Two of the 12 cats developed mild ionized hypocalcemia at 6 months of treatment. We have followed some IHC cats undergoing alendronate treatment for over 2 years without reported clinical side effects.36 The safety of oral alendronate treatment for cats with IHC and CKD has not been specifically studied, but we have not observed any documented decreases in renal function that we could attribute directly to the alendronate. Drug-induced esophageal damage (erosive esophagitis and esophageal stricture) and gastritis are of concern in humans taking oral bisphosphonates.39-42 We have not observed the development of these lesions, nor have they been reported by others, following oral alendronate treatment in IHC cats.

An increased risk for bone fracture has been reported in humans on long-term bisphosphonate treatment presumably because of the increased brittleness of bone due to bisphosphonate therapy.43 Bisphosphonate treatment in humans generally does not exceed 3 years due to concerns that acquired bone pathology outweighs previous benefits.44 We have become aware of two cats that developed pathologic fractures following 9 and 5 years of treatment with weekly oral alendronate.

Any food in the stomach can drastically reduce the absorption of alendronate to near zero – bisphosphonates are poorly absorbed at best under optimal conditions. To maximize intestinal absorption of alendronate, we recommend fasting cats overnight for 12 hours prior to the administration of medication, giving the pills in nothing other than tap water, and then feeding the cat two hours later. Though not specifically studied, an 18-hour fast prior and 4-hour fast post-pill might be a better protocol to achieve the highest possible intestinal absorption.45 We do not recommend the administration of alendronate in pill pockets due to concern about decreased intestinal absorption that could occur. For the same reason, we do not recommend alendronate that has been formulated by compounding pharmacies in flavored solution or suspension.

Given the risk of esophagitis and stricture associated with oral bisphosphonate treatment in humans, we advise extra caution to prevent esophageal tissue damage following oral alendronate administration in cats. The starting dose is usually 10 mg/cat (NOT per kg) per week initially. We recommend administration of whole tablets only, as cut tablets may increase exposure of the esophagus and stomach to adverse effects. We recommend “buttering” the cat’s lips/nose as this has been shown to increase salivation and swallowing which contributes to decreased transit time and less time for mucosal contact from the pill.46 The effect of butter on intestinal absorption of alendronate has not been specifically studied, but use of butter as part of our treatment protocol has effectively
Some cats return to normocalcemia on 10 mg oral alendronate per week, whereas other cats require dose escalation to do so. If the ionized calcium remains above the reference range at the 4 to 6 week visit, increase the dose to 20 mg once each week, or alternate giving 10 mg one week followed by 20 mg the next week to provide an average of 15 mg per week. Once the ionized calcium enters the reference range, we recommend reevaluation in 1, 3, and 4 to 6 months if the ionized calcium remains stable within the reference range. Many IHC cats return to normocalcemia following a 10 mg once weekly dose of oral alendronate, whereas some IHC cats will require 20 mg weekly to achieve normocalcemia.Rarely, 30 or 40 mg/cat/week oral alendronate will be needed to restore normocalcemia. Alendronate dose reduction should be prescribed for cats that achieve very low reference range ionized calcium in order to prevent the development of overt hypocalemia. For cats that develop overt hypocalemia, alendronate treatment should be discontinued, at least temporarily.

When should bisphosphonate treatment be stopped for IHC cats?
Alendronate treatment should be stopped in IHC cats that fail to regain normocalcemia despite 30 to 40 mg weekly doses after ascertaining strict adherence to the pre-pill fasting protocol. Alternatively, prednisolone can be added on top of alendronate to see if a beneficial effect can be gained to lower circulating calcium during combination therapy.

It is not known how long oral alendronate treatment should be continued in those IHC cats that have regained normocalcemia for long periods of time. It is possible that the salutary effects to keep circulating calcium concentrations within the reference range may last long after alendronate is discontinued due to its long half-life in bone, but this has not been specifically studied.

Though bisphosphonate treatment is very often effective in restoration of normocalcemia in IHC cats, it would be far preferable to find the underlying cause(s) of IHC so that drug therapy would no longer be needed. Guidelines as to how long bisphosphonate treatment can safely be given to cats with any disease have yet to be established. We are concerned that some cats are now receiving bisphosphonate therapy for years that may be detrimental to the cat’s long-term bone health (based on emerging reports of pathological fractures in some cats). It may not be enough to just monitor calcium and renal function status in IHC cats during treatment interventions. The measurement of calcium regulatory hormones (PTH, calcitonin, calcidiol, calcitriol, 24,25(OH)2-vitamin D, FGF-23, Klotho) before and after treatment interventions will likely reveal important components for the pathophysiology of IHC in cats and may provide targets to be altered during therapy, and also information to ensure long-term safety. Our new recommendation is to include baseline long bone radiographs for all IHC cats being treated with oral bisphosphonates for more than one year, and then yearly thereafter to more readily detect early bone injury that may be developing. Long-term safety studies in cats treated with oral alendronate are needed.

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Navigate Bumps in the Road:
Steps to Create a Thriving Cat Friendly Practice

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The single biggest opportunity to grow small animal practices lies in the chronically underserved feline patient. With nearly 1500 participating practices there is emerging a body of knowledge that is critical for prospective practices to understand. Overcoming resistance on the part of unconvinced staff members and building a team to accomplish Cat Friendly designation are critical to accomplishing the establishment-wide changes that improve the experience that cats and their owners have. 83% of adopted cats are seen within the first year of adoption. Fewer than 50% of those return for regular veterinary care. Based upon HSUS adoption data, approximately 1.7 million cats are seen once and do not return. If 3000 practices became Cat Friendly Practices and the population was divided equally among them, there would be over 550 new patients per practice per year.

The Bayer Veterinary Care Usage Study 3 – Feline Findings focused on the population of cats and their owners that do not seek regular veterinary care and the views veterinarians and practice owners have of this underserved population. More than half of these 401 practice owners reported less than 70% of appointment times were filled. This represents a significant opportunity to better utilize veterinarians, professional staff and improve the work flow of the practice. When asked what could impact growth, the top two choices were increasing cat and dog visits. However, more than 50% had no method in place to monitor or evaluate the efficacy of their reminder systems. They did not, then, know whether their existing clients were being effectively encouraged to return to the practice.

While increasing cat visits was the second most cited way to grow and practices did not believe they would need to make many changes in the practice to increase visits, less than 1 in 5 had actually taken any steps to do so. More than 1 in 3 practice owners had no intention of implementing changes that would reduce stress for cats. Almost as many had made no attempt to train staff to make feline visits less stressful.

As research has shown, there are more companion cats than dogs. This should mean that veterinary practices see more cats than dogs, but the opposite is true. Many cat owners avoid veterinary visits for a variety of reasons. One major reason is that they are convinced that their cat hates the experience. Another is a lack of understanding of the need for preventive health care for creatures who seem to be independent and healthy. Clients also dislike the experience of the 30+ minutes that precede the visit during which conflict arises around the carrier, the traumatic experiences in the automobile and the disruption of routine that is so important to cats.

Cats seem to experience forceful handling by their otherwise predictable and beloved human as a betrayal of their trust. The car, carrier and veterinary establishment are unfamiliar to a creature who values a sense of control and familiar routine. As a veterinary team, we may not understand cats, their behavior cues, or normal behaviors. We may feel as if cats are more of a nuisance, take too much time or will potentially cause injury. Our attitude is conveyed through approach, body language and other forms of communication apparent to both cats and their owners.

When a cat visit becomes disruptive we lose the fundamental opportunity to form the trusting relationship we need to have with our clients so that we can practice the best medicine. We lose the chance to calmly build rapport, establish trust and educate clients that is so crucial to our future with them and their cat.

The solution to declining cat visits, to resulting welfare issues, and to our ability to serve this patient population is to become cat friendly. We must create a practice culture in which the entire staff is committed to improving the experience of the feline patient and their owner. We must incorporate this into staff training and education, into the practice physical environment and into our plans for the future.

We must begin by educating our clients. By sharing with them our knowledge of the characteristics of the feline, we can teach them to have reasonable expectations, to understand the subtle signs of illness, and to prevent unacceptable behavior before it starts. By understanding the social groups in multiple cat households and how the social structure of cats has evolved, we can decrease the stress experienced by companion cats and their owners. We can teach breeders and “accidental” breeders to raise well-adjusted flexible, social kittens who will become wonderful cats for the people who adopt them. We can teach them how to lower the household stress by giving them a better understanding of their cats’ needs, sensory awareness, and perception of safety.

Our outreach has to be where our clients are, i.e., on the internet. We need lively web sites with important educational links. We need Facebook pages that are constantly updating and providing tips and entertaining topics that engage the clients before we meet them in the practice. Our educational efforts can result in happier households and healthier cats. Clients need to understand how cats prefer being alone when eating, why play is important and how cats interact with each other and humans.
The Bayer Brakke study showed that the recession did not cause the decline in visits but rather, unmasked a phenomenon that has been going on since the late 1990’s. This investigation made several recommendations regarding the goals that would improve cat visits including understanding the client household, addressing handling, communication, and safe transport.

Becoming cat friendly is not a construction project; it is seizing this opportunity to harness the talent and intellect of the staff to change behavior and attitudes. Cat friendly practices nurture relationships with clients by employing open communication and active listening. The staff becomes deeply committed to achieving skills in gentle handling, understanding behavior, and the unique medical and surgical needs of cat patients.

Change in the busy veterinary practice is difficult. One of the most important roles in affecting the practice culture is to assign a Cat Advocate to the project. That person is not responsible for doing all the work to become cat friendly but to make sure the work is done. Cat friendly is not a project, it is a cultural shift within the practice that must be continually monitored and assessed. Education plans, physical changes, communication training are ongoing. By evaluating the cat and client’s experience from before the visit to the time they leave, we can establish a plan for improving that experience.

The first experience of the practice environment is often the first phone call. Using that contact to educate clients or potential clients about resources available to help make the pre-visit experience less stressful are key. Questions about carriers, automobile transport and other cats in the household can be satisfactorily answered. Resources can be sent in a variety of ways from web links, pdfs or written brochures.

The physical presence of other animals in the reception area is a key consideration for reduction of stress. Many strategies for reducing the negative effects can be implemented including, separate entrances, separate waiting areas, or “cat only” days. Voices should be kept low, sounds kept to a minimum, unnecessary odors like perfume or cologne avoided. Visual barriers can be employed to keep cats from seeing dogs or other cats. Staff members must be counseled not to look directly in the face/stare at cats.

In the exam room, the cat should be allowed to walk out of the carrier while the doctor is speaking calmly with the client. If the cat leaves the carrier, remove it from sight as it has become the most familiar thing in the room and the cat will be inclined to return to the carrier. If, after an appropriate time, the cat remains in the carrier unwilling to exit voluntarily, remove the lid of the carrier. This is far less stressful than other ways of removing the cat. Towels can be employed to help fearful cats remain calmer.

One of the most critical skills required for becoming cat friendly is to learn to read how cats communicate their emotional state through their body posture, facial expression and movement. Fear is the #1 cause of “bad behavior” in the veterinary environment. By learning to assess emotional states, we can avoid a fully aroused state that takes a cat 30-40 minutes to recover from. Cats leave behind a scent from their pads that indicates stress. Careful cleaning between appointments is not only important for disinfection but also to remove this form of communication between cats.

A cat examination room should contain all of the equipment and supplies needed to perform most outpatient services. By approaching in a calm manner, keeping the people in the room to a minimum, using quiet voices, towels for restraint if needed, and being flexible about the order the exam is performed in, there will be more successful experiences than usual. Scruffing or stretching should never be necessary and is counter-productive. In a calm environment the doctor can talk through the exam, making sure clients understand what is being done and the value and importance of the physical exam.

Many gentle techniques are described in the photos in the Cat Friendly Practice (CFP) program that offer ideas regarding restraint. The examination table may be the least necessary piece of equipment in the room. Cats may prefer the bottom of a carrier, a lap, a chair or the floor and should be accommodated. Moving cats by picking them up adds a level of stress to an already fearful cat. The reflex response to fear is to flee thus maintaining all four feet on the floor is very important to a sense of control and reassurance. Every effort should be made to avoid taking the cat to the “back” of the hospital. The exam room is now somewhat familiar. To move to a foreign space offers new stressors, different smells, bright lights, more animals, people, and noises.

Cats who must be admitted to the hospital have an increased need for a sense of familiar comforts. This can be provided by asking the client to bring known items from home; bedding, brushes, food, bowls or toys. Soft bedding, a place to hide and gentle nursing techniques are critical. For cats who enjoy social interaction, petting, brushing and other forms of interaction can be employed.

The cat ward should be separate from dogs and other animals, big enough so that cats cannot see one another. Cages should not face each other. Cats passing each other for treatment or discharge should be shielded from view. When removing a cat from a hospital enclosure, allow the cat to come forward or use bedding, towels or the bottom of the carrier to slide the patient forward. Do not loom about the cat or block the light.

The entire inventory of equipment, instrumentation, physical facility should be examined to make sure they are appropriately sized for the feline patient.

The Cat Friendly Practice program provides veterinary practices with ALL of the information, tools and techniques for becoming cat friendly. There are ten areas to evaluate with resources to achieve compliance with all of them. This program will continue to evolve and grow as new phases are implemented. The next of these will be Preventative Health Care. To participate the practice must
have one AAFP member, identify the Cat Advocate for the practice and use the website, manual and checklist to achieve either gold or silver CFP status.

In recognition of this effort, the program provides you with a toolkit to market your practice as one that has made this significant effort and to distinguish yours from other practices that have not. A searchable website will allow clients to look for Cat Friendly Practices in their region. Beginning in the fourth quarter of 2012, the AAFP began a national consumer awareness campaign to encourage cat owners to seek a Cat Friendly Practice. Refinements and additions to this campaign will continue.

As we discuss each aspect of the program, specific examples of creative and innovative methods CFP practices used to overcome barriers to certification, to market themselves and to significantly benefit by the effort made to implement the program will be discussed. Almost every CFP practice currently certified plans to renew their certification when the two -year membership period expires. Recertification is intended to reinforce the CFP concepts and to introduce new tools and resources made available since the program began.

The CFP task force and internal team are continually analyzing the feedback from member practices, both designated and working on becoming so. Based upon that feedback there are videos directed at both the veterinary team and clients to demonstrate techniques important to improving the experience. New tools are being developed throughout the year to meet their needs for social media, staff meetings, owner education and staff development. In 2015, the task force and AAFP board will create a strategic plan for the future of Cat Friendly Practice. It is our intention to keep evolving the program to add value to participating practices, to create tools and resources for practices to attract cat owners and to drive cat owners to practices that participate.
In human medicine much research has occurred regarding the “Patient-centered Interview”, resulting in evidence based method used to train medical students, nurses, physicians and other health care workers who must have a successful interview with a patient in order to assure the best possible outcome. This evidence based approach to patient interviewing has valuable parallels in our desire to build trusting relationships with our clients.

With client-centered skills, we encourage them to express what is most important to them. This approach recognizes the importance of their personal concerns, feelings, and emotions. The patient is not isolated from its context. For example, a patient of mine recently presented for inappetance, lethargy and icterus, which the owner thought, had only developed in the last 2 days. This client is a very aware client and one who recognizes the subtlety of feline symptom exhibition. It was clear, however, from the physical exam that this patient had been ill for quite a bit longer than the owner thought. After we talked for awhile, she shared with me that her husband had an inoperable tumor and was about to start a new round of chemotherapy and radiation before referral to a tertiary hospital for very complex surgery. My patient’s condition was clearly a part of a complex emotional time for this owner. She said, too, that her cat was the one who gave her the love and affection she needed when she was upset by everything that was arising and that she could not bear to lose her. The emotional context and family circumstances are often part of the reason a cat is presented to us and we need to be able to elicit and understand them. The level of satisfaction a client will express is directly associated with feeling understood.

Clients usually have more than one concern. Indeed the first concern mentioned may not be the most important one to the client. Sometimes the last concern raised is the most important one but was saved for last because it is the more frightening or sad. By asking the right kind of questions, we can be sure that we understand the whole story. It is also therapeutic for the client to tell their story rather than be asked a series of questions. It can be cathartic. Most of us have experienced feeling unburdened and less alone after sharing a story of difficulty with a good listener. Our clients don’t expect us to “fix” everything. They understand that we cannot. Sharing the struggle a client is experiencing and responding empathetically is often enough.

Three broad types of skills need to be addressed in communication skills training:

1. Content skills – what we communicate. The substance of clients’ questions and our responses, the information we gather and give, the treatment plans we discuss
2. Process skills – how we do it. The ways we communicate with clients, how we discover history, provide information. The verbal and nonverbal skills we use, how we develop a relationship with the client, the way we organize and structure communication

Perceptual skills – what the clients and we are thinking and feeling. The internal decision-making, clinical reasoning and problem solving skills we bring to the encounter. Our attitudes, personal capacities for compassion, mindfulness, integrity, respect and flexibility are critical to understanding how to create a successful relationship and achieve the best outcomes. We need to be aware of our feelings and thoughts about the client, about the patient’s condition and other issues that may be concerning the client; awareness of our own self-concept and confidence, of our own biases and distractions.

It is important to emphasize that content, process, and perceptual skills are inextricably linked and cannot be considered in isolation.

In 1998, the Calgary-Cambridge guide was created to provide a structure for teaching and learning communication skills. It provided a comprehensive repertoire of skills validated by research and theoretical evidence. It provided guidance on skills that make a difference in medical communications. In 2003, enhancement to the guide were developed which visually and conceptually improved the way communications skills training took place. Three diagrams helped to place the skills in relationship and context. With this enhancement came a new content guide for skills training. Since then communication experts in veterinary medicine have utilized this evidence based approach to adapt the guide to client communications. Studies in JAVMA since 2001 have demonstrated strong evidence of the value of this approach over the paternalistic approach favored by physicians in the past. For example, a study published in JAVMA in 2012 demonstrated a clear relationship between client compliance and satisfaction with their relationship with the veterinarian.

References
In both people and companion animals, cachexia and sarcopenia are 2 important syndromes that occur in a variety of chronic diseases and aging, respectively. Although cachexia has been recognized in people for over 2,000 years, only recently has it become acknowledged as a common and detrimental finding that is associated with increased morbidity and mortality, and with this observation has come rapidly expanding interest and research. Both of these syndromes are becoming increasingly important in human and veterinary medicine because of their high prevalence and adverse clinical effects, and a better understanding of the mechanisms underlying these syndromes is critical for optimal patient care, whether human or veterinary.

Cachexia is defined as loss of weight and muscle mass secondary to chronic inflammation or disease. Sarcopenia, “poverty of flesh”, is an age-related loss of lean body mass. Sarcopenia is not caused by disease, is a gradual process and progresses with age. Loss of muscle can occur without fat loss or a decrease in Body Condition Score (BCS). Individual cats, particularly those with long coats or a history of obesity may appear to have a high BCS and yet be under muscled.

One of the keys to the management of cachexia and sarcopenia in dogs and cats is recognizing it in its earliest stages. To achieve this, BCS and Muscle Condition Score (MCS) must be consistently assessed. The goal for BCS in a healthy cat is 4–5 on a 9-point BCS scale. However, in certain diseases (eg, CHF, CKD), a slightly higher BCS may be desirable (ie, a BCS of 6–7/9), although further research is required to make specific recommendations. Even in animals with these diseases, obesity (BCS > 7/9) should be avoided.

The MCS differs from the BCS in that it specifically evaluates muscle mass. Evaluation of muscle mass includes visual examination and palpation of the head, scapulae, epaxial muscles over the thoracic and lumbar vertebrae, and pelvic bones.

In people, the loss of LBM has direct and deleterious effects on strength, immune function, wound healing, and survival. In fact, cachexia is an independent predictor of survival in people. The specific deleterious effects of muscle loss have not been as well studied in dogs and cats although there are studies associating thin body condition with decreased survival.

The weight loss that occurs in cachexia is unlike that seen in a healthy animal that loses weight. In a healthy animal that is receiving insufficient calories to meet requirements, metabolic adaptations allow fat to be used as the primary fuel source, thus preserving LBM. Conversely, acute and chronic diseases alter concentrations of a variety of mediators (eg, inflammatory cytokines, catecholamines, cortisol, insulin, glucagon), which then decrease the ability to make metabolic adaptations required to switch to fat utilization, and amino acids continue to be used as a primary source of energy. Therefore, muscle and LBM quickly are catabolized.

Numerous other factors can contribute to muscle and weight loss. Maintenance energy requirements vary with age, genetics, health status and gender (intact or altered). In presence of some disease states, maintenance energy requirements increase significantly. Decreased nutrient absorption is another possible mechanism for muscle loss in cachexia and sarcopenia. Studies in cats have shown decreased digestive ability. One investigator showed a reduced ability to digest protein in 20% of geriatric cats with about 33% having a significant reduction in ability to digest dietary fat. Micronutrient absorption, potassium, phosphorus, sodium, choline, B vitamins and Vitamin E, is also decreased.

Cats derive most of their energy requirements from protein and are metabolically less able to handle decreased amounts of protein and increased amounts of carbohydrates to maintain their energy requirements. Omnivores adapt to lower dietary protein by down regulation of their protein metabolism (protein sparing) but cats have been proven to be unable to make this physiologic adaptation. This preferential use of protein for energy can have clinical effects when cats are ill or anorectic as protein malnourishment can occur.

An important problem in cardiac and other forms of cachexia is a decreased calorie intake. The anorexia may be secondary to fatigue, dyspnea, or may be because of medication toxicity or alterations in appetite that often accompany CHF, cancer, and CKD in cats. Absolute food intake may decrease in animals with these diseases, but there also may be altered food preferences, cyclical appetite, and other issues that negatively affect overall food intake. Anorexia, for example, is present in 34–84% of dogs and cats with heart disease.

Increased energy requirements, alterations in nutrient absorption, and decreased energy intake all likely play important roles in the pathogenesis of cachexia by causing a net calorie deficit. However, a healthy animal that has a calorie deficit, either as a consequence of decreased food intake or increased energy requirements, would primarily lose fat. Therefore, these factors are not sufficient to explain the muscle and LBM loss and relative sparing of fat that are the hallmarks of cachexia and sarcopenia. This discrepancy suggests that metabolic alterations also are present.

Because of the important implications of cachexia and sarcopenia on morbidity and mortality in people, there is now extensive research into the prevention, diagnosis, and treatment of these syndromes. There are exciting opportunities for new and effective
targets to decrease energy requirements, enhance energy intake, improve nutrient absorption, and modify metabolic alterations to prevent and even reverse the effects of both cachexia and sarcopenia.

A 2008 study on longevity in aging cats studied in a controlled environment for 5 years showed that all cats lost weight over time. However, cats supplemented with dietary antioxidants, prebiotic chicory root and a blend of Omega 3 and 6 fatty acids had a beneficial effect over a commercially fed diet alone or one supplemented only with antioxidants (Vitamin E and beta carotene). Cats in the fully supplemented group lost less weight, lived longer, had better LBM scores, improved fecal flora and fewer diseases.

In many cases, practical methods to help owners manage their animal’s appetite are critical to success. This is particularly important because anorexia is one of the most common contributing causes to an owner’s decision to euthanize his or her pet.

Any issues that potentially can affect food intake should be addressed, whether physical or environmental. Dental disease, for example, can substantially impair food intake in an otherwise healthy or sick animal. Pain (eg, back or joint) can decrease an animal’s mobility and make it more difficult to secure adequate food intake. Environmental issues also can negatively impact food intake. Multipet households may impede the ability of an individual animal to gain access to food (eg, a more frail or timid animal may be crowded out from the food bowl). Stress often can increase for animals after diagnosis of any illness because of lifestyle changes (eg, medication administration, new foods), as well as increased stress on the part of the owner, which may be detected by the animal.

Once environmental issues are ruled out as a cause of weight loss, a nutritional screening is crucial. Older cats may need 5-6 g of protein/kg to prevent protein catabolism. Reduced digestive ability indicate that a high energy, highly digestible diet may be needed. Some kitten formulas may be more appropriate. Folate and cobalamin supplementation may be useful. Commercial cat foods vary quite widely in caloric density. Specific formulas should be investigated for adequacy.

Cachexia should be anticipated in animals with chronic diseases such as CHF, CKD, cancer, and others. Consistently evaluating MCS in all patients will help identify muscle loss at an early, mild stage in aging or ill animals, rather than waiting until muscle loss is moderate or severe, when it may be more difficult to successfully manage. Similarly, as animals age, muscle loss is likely to occur, even in healthy individuals. Therefore, muscle mass should be thoroughly evaluated in geriatric cats and dogs.

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http://www.wsava.org/nutrition-toolkit
Old age is not a disease. Both veterinarians and owners must resist the temptation to ascribe signs of illness to aging. Some signs of illness such as chronic pain, dehydration or hypokalemia may lead to clinical signs that owners ascribe to “slowing down” with old age. Many problems of senior cats are chronic and progressive so that early diagnosis and treatment is important for pain management and quality of life. It can also be tempting to find a “diagnosis” and treat for that without continually evaluating the “whole” cat. The focus on a single diagnosis and treatment plan can neglect common comorbid conditions that can dramatically affect quality of life. A hyperthyroid cat, for example, may suffer from other conditions more common in older cats; overgrown nails, decreased olfactory sensing, which can impact appetite, muscle atrophy and osteoarthritis or periodontal disease.

For these reasons and a host of others, comprehensive wellness examinations, history assessment and a minimum database are recommended every 6 months for seniors. Health status may change rapidly in this group and early detection and treatment is important to preserve quality of life. Signs of illness in cats are often quite subtle and easy for owners to overlook. The minimum database includes a complete blood count (CBC), a full serum chemistry panel with electrolytes, a full urinalysis and total T4. Early detection of a decline in renal function will be found in declining urine specific gravity before BUN and Creatinine are beyond the normal range, making the urinalysis a critical part of information gathering. Depending upon risk factors, fecal examination and retrovirus testing may also be indicated. Blood pressure measurement should also be included in any cat with known risk factors. Because senior cats’ response to vaccination is largely unknown and immune function may be affected by both aging and the presence of chronic disease, vaccinations should be given according to the AAHP Feline Vaccine Advisory Panel for all cats.

The home environment is critical to wellness. Staff members should be trained to educate owners about enrichment, stress identification and modification for aging changes. Senior cats may benefit by an additional heat source such as a heated bed or one placed close to a heat source. Resting or hiding areas that are inaccessible to other pets, quiet and easily accessible for the senior may help with stress reduction. Litterboxes should be large and shallow with low sides and placed in quiet locations. If the home has multiple stories, boxes should be placed on each. Night-lights may be helpful with declining vision. Multiple fresh water sources can encourage moisture consumption in cats that may be prone to dehydration because of reduced urine concentrating ability.

In senior cats, cognitive dysfunction (CD) is now recognized as an important problem. Formal diagnostic criteria have yet to be established. It is a diagnosis of exclusion. The most common signs are disorientation in time and space, altered learning, house soiling, altered interactions (e.g. attention seeking, anxiety, irritability) changes in activity (wandering or pacing) changes in sleep patterns, decreased appetite, decreased grooming and increased vocalization. Medical problems such as hyperthyroidism, hypertension, pain of osteoarthritis, or chronic kidney disease can mimic many of these signs and so must be excluded before presuming CD.

Published studies are lacking on the efficacy of treatment. Therapies extrapolated from studies in humans and dogs include antioxidant enriched diets, supplements phosphatidyserine, omega-3 fatty acids, Vitamins E and C, L-carnitine. One ingredient found in supplements for dogs, alpha-lipoic acid, is toxic in cats. SAMe improved activity and awareness in dogs and is commonly used in cats with hepatic disease. No trials with these supplements have been published for cats with CD. Therapies for cats with CD are anecdotal.

There is evidence of cholinergic decline in senior cats so drugs with anticholinergic activity (e.g. some SSRIs such as paroxetine and TCAs) should be avoided. Selegiline (Anipryl), which has been anecdotally reported to be useful in cats and proven beneficial in dogs for CD, should not be combined with SSRIs or TCAs. Environmental enrichment and Feliway have often been recommended but no studies in cats show benefit. In fact, in cats with CD modifications to the environment may be detrimental. Regular and predictable routines are most desirable. Any changes should take place slowly.

**Hyperthyroidism and chronic kidney disease (CKD)**

The presence of these occurring concurrently affects not only the diagnosis but also the treatment and prognosis. A more cautious approach to treatment is required. The relationship between the two is not known. Hyperthyroidism may damage the kidneys or the consequent hypertension may contribute to renal damage. Hyperthyroidism seems to mask a decline in renal function by increasing renal blood flow and hence glomerular filtration rate (GFR).

Diagnosis is complicated by the suppression of thyroid hormones by a concurrent illness or “sick euthyroid”. Cats with both an upper reference range normal Creatinine and TT4 are likely to have both hyperthyroidism and CKD. A TT4 can be repeated in a few weeks or a free T4 by equilibrium dialysis can be done though it carries a slightly higher risk of false-positive results. The presence of CKD can affect hematology results. Erythrocytosis occasionally seen in hyperthyroidism may be masked by anemia of CKD.
Presently the assessment of kidney function depends upon elevated BUN and Creatinine with a reduced urine specific gravity. However concentrations of BUN can be increased by the polyphagia of hyperthyroid, Creatinine reduced because these cats are thin and have lost lean body condition, while increased GFR can reduce both. Urine specific gravity can be low because of either disease; both increase the risk of urinary tract infection.

All treatments for hyperthyroidism can worsen kidney function. Hyperthyroidism increases renal blood flow and GFR. Treatment may lower GFR by up to 50%, which may unmask previously unrecognized kidney disease. Treatment may initiate a crisis. Affected cats become azotemic and may start to show significant decreases in renal function by 4 weeks of treatment. No significant differences in pretreatment parameters have been shown between cats that will become azotemic after treatment and cats that will not. GFR, iohekol clearance and other assessment tools are not readily available in practice yet.

For these reasons, treatment with medical management for all cats should precede any other form of therapy. Medical management is reversible, can be reduced, and induces euthyroid states more gradually. Radioiodine and surgery may result in acute destabilization. Medical management should continue for a period of time, months before considering curative, permanent treatments.

If a cat is known to have CKD at the time of diagnosis, treatment with a lower dose of medication should be given at the start. For methimazole, 1.25mg- 5 mg once daily with frequent checks of renal parameters, titrating the dose upward. Renal parameters should be monitored at 3 and 6 weeks following start of therapy.

Attaining a euthyroid state should be the goal unless this level of thyroid hormone worsens renal parameters. Ongoing management should aim for a balance between the two conditions. Individual response to therapy should guide treatment. For example, if euthyroidism causes significant renal dysfunction, suboptimal control of hyperthyroidism may yield a patient that maintains weight and body condition.

**Heart failure and chronic kidney disease (cardiorenal syndrome or CRS)**

In the cat, the incidence of chronic abnormalities in cardiac function (e.g. congestive heart failure) causing progressive and permanent chronic kidney disease is unknown. A study of 102 cats with hypertrophic cardiomyopathy reported 59% prevalence for azotemia as compared to 20% for age-matched controls.

CRS occurs when worsening renal function limits diuresis despite clinical volume overload associated with heart failure. In cats being treated for chronic heart failure, declining renal function should be anticipated. The diagnostic marker for CKD, isosthenuria, cannot be relied upon in cats being treated with diuretics. Monitoring of Creatinine especially should be used to discern trends in renal function. A progressive rise even within the normal range should alert the practitioner, along with clinical signs: PU/PD, hyporexia, anorexia, weight loss and vomiting.

A minimum database should include abdominal ultrasound to assess for typical changes in renal architecture and to identify underlying causes that may have specific treatments, such as neoplasia, pyelonephritis, and nephrolithiasis. Blood pressure monitoring should be included as well as hypotension from therapy can decrease renal perfusion. The usual diagnostic imaging; echocardiogram, thoracic radiographs are important for type of cardiac disease, risk assessment, and treatment planning.

Goals of treatment are to recognize CRS, reverse it as much as possible and deal with the renal consequences of heart failure and the complex relationship between heart failure and renal injury. The difficult balance is to “dry out” the heart failure and hydrate the kidneys. Different therapeutic strategies are based upon the degree of compromise of each organ.

Ace inhibitors are the mainstay of therapy for CRS especially in the presence of hypertension or proteinuria. Cats with CRS should be hydrated before starting therapy. Low dose benazepril or enalapril 0.25mg/kg Q 24 hours can be increased to proved better control for heart failure. Benazepril is metabolized in the liver, Enalapril in the kidneys. Therefore, cats with CRS may need a lower dose of enalapril than benazepril. Initiation of therapy may show a transient increase in BUN/Creatinine concentrations. If persistent, lowering the dose is usually sufficient.

If azotemia is becoming a concern, the first step is to lower the dose of diuretics. The goal is to find the lowest effective dose that controls heart failure. The dose must be continuously reassessed. The ideal dose for an individual patient achieves the threshold rate of drug excretion. An individual HF patient that is not responsive to 5mg of furosemide per 24 hour for example will need 10 mg per 24 hours, not 5mg every 12 hours. Adequate natriuresis can be grossly assessed by observation of increased urine volume and decreased specific gravity. Periodic drainage of pleural fluid or ascites can be used to avoid excessive diuretic use.

In the event that diuretic resistance occurs, several options are available to correct fluid balance. A CRI of furosemide (0.3-0.6mg/kg/hour IV inhibits sodium resorption more effectively than oral or IV Boluses. Once the volume overload has resolved, most cats will again respond to oral therapy. Another loop diuretic, torsemide has superior diuretic action and long half-life. (0.3mg/kg PO Q 24 hours) It appears to be 10 times more potent than furosemide. Dual-diuretic therapy can be considered when furosemide dose needs to be decrease. Spironolactone (1-2 mg/kg Q 12 hours) may cause severe facial pruritus and must be used with caution. Aldosterone sometimes causes significant hyperkalemia. Each work at different sites within the nephron and if tolerated may be helpful.
Systemic hypertension is common in CKD and by increasing afterload increases the cardiac workload. Hypertension worsens both CKD and heart failure. If present, amlodipine (0.625 mg/cat PO Q 24 hours) should be added. Blood pressure monitoring is critical to avoid the effects of iatrogenic hypotension.

In advanced CRS, a positive inotrope (pimobendan) may improve azotemia, demeanor and appetite and allow reduction in diuretic dose.

Dietary modification should consider both conditions. Sodium restriction is sometimes needed and the extent to which it is required will vary. Distilled or low sodium water may be offered for drinking if more sodium restriction is needed than can be provide with diet. Clients should be cautioned not to feed high sodium treats. Lower phosphorus diets may be helpful in managing kidney disease but may result in the loss of lean body condition. High quality protein should be given to the level that it does not worsen azotemia. Omega-3 polyunsaturated fatty acids have been shown to be beneficial in both cardiac and renal conditions. Many renal diets are supplemented or if given separately EPA 40mg/kg/day, DHA 25mg/kg/day.

Fluid administration is a balance between improving renal blood flow without precipitating congestive heart failure. Fluids should be given slowly to correct azotemia, tailored to the individual’s ability to tolerate. Abrupt changes in weight, a new gallop heart sound and/or heart rate may indicate impending congestive event and justify fluid rate reduction. Sometimes a low-dose CRI of furosemide will be indicated concurrently in cats with end-stage CRS. SQ fluids may be less likely to trigger a congestive event and can be given every 24-48 hours via a balanced electrolyte solution and adjusted to the individual patient’s ability to tolerate. In fragile patients, a smaller volume of fluids, as little as 30mls every 48 hours may be necessary, titrating slowly upward if the expected effect on uremia is not evident. Electrolytes should be monitored closely, especially potassium, as hypokalemia can trigger arrhythmia. Correction can take place through fluid therapy or oral means.

Although renal function may remain stable for a period of time in cats with heart failure, when CRS occurs it leads to frequent hospitalization, difficulty maintaining good quality of life and eventually euthanasia. The therapy described here is directed at improving quality of life for cats with CRS. Whether they contribute to prolonged survival is unknown.
In an AVMA sponsored conference on euthanasia, slaughter and depopulation called “Humane Endings” in October, 2014, the keynote speaker described the change in public perception of the importance of animals of all kinds. He described the increasingly pervasive public perception of animals as connected to humans and the associated increased public aversion to animal deaths and killing. He concluded that animal death and killing will become more emotional and more contentious. While his remarks were directed at all the participants, the implications for the experience clients have of euthanasia are clear. Our obligation to provide a painless death for the beloved animal and an acceptable experience for owners of companion animals is becoming more complex.

With the decreasing nuclear family, an outcome of the decline of agricultural community, the rise of industrialization, climbing divorce rates and prolonged life spans, comes the increase in isolation from family, neighbors and community. Yet people need love, companionship and emotional support. This has given rise to the redefinition of pets as family members. About 90% of respondents in one study of 100,000 US households rated a pet as important or extremely important to the family. For many complex reasons, the emotional attachments which many humans develop for their pets not only equals but frequently transcends the emotional attachment which they form with humans and can be a source of unconditional love, support, comfort, safety, security and stability.

When highly attached owners recognize that a moment has arisen in the clinical management of a life-limiting medical condition when a cure is not an attainable goal, it is normal for them to experience strong emotions, generally termed anticipatory grief. Anticipatory grief is the psyche’s way of preparing for impending loss. This is often the beginning of a period of powerful emotional states which can blur judgment at a time when clear thinking and planning may be key to resolution of grief and ending the suffering of a beloved pet.

Pet owners often trust veterinarians and/or see them as authority figures. During loss, clients may look to the veterinarian to provide strength, guidance, leadership. Given clients expectations and the impact of end-of-life conversations on pet owner and the veterinary team, compassionate communication should be considered both a core clinical skill and an ethical obligation for veterinarians.

One core belief that must be developed in clients is that preserving quality of life takes precedence over measures to prolong life. With the sophistication of veterinary medicine and technology comes the ability to prolong suffering by engaging in many more forms of therapy than were previously unavailable for beloved pets. Veterinarians now have to advocate for the animal interest to end a life when further intervention will cause or exacerbate suffering. This life-prolonging technology has rendered the term “natural death” progressively meaningless, giving rise to complex ethical struggles with medical futility and who decides when to pull the plug and why.

The owner becomes the animal’s proxy and will decide if and when euthanasia is a better option than life for an animal that is suffering despite receiving the best comfort care available. The strongest desire of highly attached pet owners facing the loss of a beloved pet is to do what is best for the animal. It is an elusive goal and one which requires the owner’s interpretation of the animal’s state.

A veterinarian can help by educating an owner in how to assess quality of life, attributing relative weight to specific experiences like the presence or absence of joy, pain, or frustration. In the general practitioners’ relationships with clients there is very often a long more intimate connection than there is with specialists to whom the animal may have been referred for care. Therefore, the generalist should stay involved after a referral and advocate for what is right for the pet. This is also important for the emotional state of the owner. Powerful emotions can ensue when decisions are second-guessed. Decisions made too early may cause profound guilt. A decision thought to be made too late may be interpreted as causing suffering for a beloved family member. The uncertainty that is a natural part of being a proxy for another’s best interest is always present.

In the best possible situation, before the anticipatory grief has begun, Quality of Life considerations are best made, once a trusting relationship is built between a client and the veterinarian. A journal kept from the time a potentially life-threatening condition has been recognized can be helpful in recognizing the balance between levels of happiness and distress based upon the behavior of the pet. Since there are no generally acceptable lines between what is acceptable and not acceptable Quality of Life, the individual observations can help reduce the burden on the client. We must build the client’s confidence that they can comprehend their pet’s condition and “walk in his shoes”. By trusting the ability of persons most closely bonded to feel in their gut what the animal is experiencing, we encourage good choices.

The skills of educating, supporting, guiding and facilitating are key to assisting the client. More importantly, the veterinarian must not try to solve the owner’s problems by making decisions for them, by giving them advice on what course they should take, rationalizing their choices or rescuing them. Presenting options gives families control over the process leading to inevitable loss by
helping them find their own view of what constitutes the best way to care for their animal. A sense of control – even if limited – has been shown to correlate with healthy grieving and emotional healing. The manner in which a veterinarian provides care for a client whose pet has died has the potential to alleviate or aggravate grief, influence client and veterinarian satisfaction and create or destroy long-lasting relationships.

It is essential to listen to what is most important to the family under the circumstances, what their concerns are, how they want to spend their time as options become limited and what kind of tradeoffs they are willing to make. The sense of control should extend to the physical and social environment surrounding a beloved pet during the last moments. Planning in advance, before powerful emotions hold sway over decisions, will allow the family to think clearly through their plan. As emotional states become more ascendant, remind the owners of their decisions. They may choose the form of death, natural or euthanasia, who should be present, the tenor of the ritual and whether children should be involved. If euthanasia is elected, the mechanics of the process should be discussed. If the client is comfortable with placement of an IV catheter or not, how to administer a sedative if one is needed and so on. The location may be of concern as well, whether outdoors, in the owner’s lap, at home, on the floor. Conventional rituals that support and comfort people at the time of the loss of a human loved one, funerals, calling hours, or celebrations of life, have not evolved around pet loss. This one event may be all the ritual possible for a highly attached client whose family may not perceive the death as a loss of a loved one.

References
AVMA Guidelines for Euthanasia; 2013 Edition
There is no question of the “growing problem” of obesity among adult cats around the world. In a study of 12 owner-owned cats in the United Kingdom, even referral to a weight loss center did not insure rapid weight loss. Many factors were found to be significant in this study, owner compliance with directions was considered one of the most significant. All cats lost weight, but more slowly than predicted. Exercise may not have been encouraged or treats may have been added. In the end, we humans are the most important reason for this dangerous trend. Of particular interest in this study was the loss of lean body mass during weight loss. While fat loss was the most significant, the loss of lean body mass meant that muscle and basal metabolic rate declined. In another study of cats on a weight loss plan, the owners of the cats who did not lose weight consistently under-estimated the body condition score of their cat. The perception of normal on the part of the individual responsible for feeding had an impact on weight management.

Because obesity is a world wide trend in both adults and children, there may be some instructive value in examining the characteristics of successful weight loss and management in humans. Those who lost weight and successfully maintained their target weight were far more likely to plan meals, measure food, track calories, plan exercise, exercise for at least 30 minutes a day and weigh themselves every day. The use of over the counter weight loss supplements was negatively correlated to weight loss. While several of these strategies may not be relevant to cats as we shall explore, the idea of tight control appears to be the most significant concept that can be derived from human research on weight loss.

Cats are obligate carnivores and as such have specific nutrient requirements that reflect their evolutionary background. The natural diet of the cat is high protein, low carbohydrate diet derived from the prey they consume in the wild.

As obligate carnivores cats differ from dogs and other omnivores in their nutritional requirements and physiologic adaptations. Cats have not developed many of the metabolic pathways for processing higher carbohydrate diets that omnivorous have and because of the lack of these pathways have different requirements in their diet than dogs and other omnivores.

Commercial dry cat foods are convenient to give to cats, many cats enjoy or even prefer them and they are tolerated well by many in cats in most situations. However, because of the inherent differences in metabolism feeding high carbohydrate diets to cats may predispose them to obesity and may also have untoward effects during times of illness malnutrition. Higher protein, low carbohydrate diets may also be more effective in managing certain diseases such as hepatic lipidosis, diabetes mellitus and obesity.

Weight reduction requirements differ between omnivores and cats and reflect the cat's inability to store excess starch as glycogen. Glucose exceeding energy requirements is stored as fat.

Feeding high fiber, low fat diets to obese cats does result in weight loss but at the expense of lean body mass. The basal metabolism of the cat may be lowered, predisposing the animal to regaining of the weight. In several studies Cats fed a high protein, low carbohydrate diet lost weight but maintained their lean body mass in comparison to cats fed a high carbohydrate low fat diet. The amount of food available to cats on such a diet should be regulated.

When feeding cats a high protein low carbohydrate diet for obesity management canned foods provide the optimal amounts of protein and carbohydrate and canned kitten food provides the closest approximation to the cat's natural diet.

Unlike dogs, 'domestic' cats are not evolved to scavenge. They have a small liver and a simple digestive system that is not able to cope with toxic or bacterial contamination. Their feeding is therefore restricted to live, healthy prey. Whilst dogs hunt cooperatively and are able to bring down prey that is much bigger than themselves, the cat, being a solitary hunter, is only able to catch relatively small prey. It also does not have pressure to share its prey with other members of its roup, because it does not depend upon them to help catch it.

The wild and feral cousins of the domestic cat spend 6–8 hours per day hunting. Of the 100–150 hunting attempts per day perhaps 10% will be successful. With a failure rate as high as this a cat may expect to have periods during which the amount of prey captured barely meets energy expenditure. On successful days the cat may catch a surfeit of food.

The result is that in the cat, hunting activity is not related to hunger or satiation. The cat would soon die if it took a break for several hours after every meal, because this would mean it would miss the best hunting opportunities. Hunting is also not related to the pleasurable taste of the prey. Small mammals and birds do not come in a variety of appetizing flavors, and in any case the cat's perception of flavor is geared to detect spoilage, not to enable it to be a gastronome.

Given the tightly regulated activity and feeding pattern of cats, and the lack of social significance of feeding, it would be expected that obesity would be unlikely in this species.

However, obesity is an increasing issue, and relates to feeding patterns that fail to take into account the natural behavior of the cat, and which are designed to satisfy human attitudes to the value of offering food as an attempt to show care.
A typical domestic cat expends very much less energy on finding and consuming food than its feral counterpart. Meals are presented in a bowl and may be consumed in seconds. No elements of the hunting strategy are activated.

In the domestic environment cats may have few opportunities to climb or explore three-dimensional space so their energy expenditure is typically very low compared to wild cats. This tips energy utilization in favor of increased storage, and hence obesity.

Cats do not go shopping, so the food we give them is designed to appeal to human shoppers and not to cats. Humans are social eaters and expect to enjoy shared meals and social interaction. Many owners expect that a happy cat is one that shows appreciation for the food we give by clearing the food bowl in the way that a person or a dog might.

Food and feeding regimes are therefore designed to reinforce these human misconceptions. Owners feed highly appetizing foods that are likely to encourage the cat to eat more than it might otherwise choose. This is much the same as the effect of intense flavor on overwhelming satiation in man. We also know that feeding multiple flavor variations of foods will increase a cat's total food intake.

Without reeducation, owners will constantly seek to 'improve' the food they give their cats so that they begin to eat in the same way as people. A meal that is not immediately consumed is taken as an indication that the cat is dissatisfied with its food.

The consumption of larger than normal quantities of food at each meal is likely to distend the cat's stomach and create the same false perception of hunger that is seen in man, the satiation of which is further reinforced by the extremely appetizing nature of the food. Most cats will approach their owners for attention or play many times during the day. Sociable cats have quite a high demand for interaction of this kind. Many of the cat's resources are focused in the kitchen area; food, latrines, cat door, etc. Cats will therefore approach their owners in the kitchen or will entice their owners there.

Unfortunately this is misinterpreted as an indication that the cat wishes to have more food. Owners will often replace old food with fresh. Given that the owner has offered no other interaction this may be attractive to the cat, which is unwilling to eat spoiled or old food. When the cat begins to eat the owner reinforces this by showing attention, or by playing a game after the cat has eaten.

In this way the cat may eat as a substitute for other activities, or may learn to eat in order to get the attention and play that it actually wanted. The cat therefore eats more than it might normally choose to, because its demands for other kind of interaction are not met, or are conditional on eating.

In addition, recent evidence indicates that owners of overweight cats interpret the needs of their pets differently from owners of cats of normal weight. Obese-cat owners do understand that when a cat vocalizes or approaches that this is for attention and social interaction. In this respect they are no different from owners of normal cats. However, they are more likely to perceive hunger in the vocalizations of cats, which drives them to offer food. This is quite similar to the way that humans interact with each other; if we have a visitor we don't assume that this person has come round to get food but we still offer it as a sign of hospitality. This is because one of the primary methods of showing care toward another person is to identify and satisfy their undeclared needs.

This appears to be at the root of the reason for why owners of obese cats find it hard to stick to diet programs. Cats may evoke a greater emotional response from some people due to the type and pitch of their vocalizations, which are more like those of a human infant. In some cases owners of obese cats can become quite distressed as a result of the emotional conflict they experience when balancing the need to diet the cat for health reasons, and the stress they experience when deliberately not meeting the animal's apparent physical need for food.

Cats do not eat as a social group, and find it uncomfortable and stressful to feed close to one another. If food is restricted to two meals per day, fed by the owner, then a group of cats will be forced to eat in close proximity to one another. This not only increases anxiety and aggression because food cannot be consumed in private, but also pressures the individual cat to eat an uncomfortably large amount of food at one sitting, because that food will otherwise be rapidly eaten by the other cats. Cats therefore eat beyond natural satiation due to the stress of reduced food availability.

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Pandora Syndrome: Not Just the Bladder Any More
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Lower urinary tract signs (LUTS) – dysuria, peruria, pollakiuria and stranguria – are a common reason pet cats are brought to veterinary practices. When presented with a cat with these signs clinicians need to know whether this is the first episode or whether it is a chronic, recurrent disease as well as what other health problems the cat may have. Armed with this information an appropriate diagnostic plan can be made.

Cats may have multiple reasons for their clinical signs as well as other medical conditions and environmental requirements that need to be addressed. For example, Buffington et al. have presented evidence that some cats with severe, chronic LUTS seem to have a functional rather than a structural lower urinary tract disorder and that peruria can occur in apparently healthy cats exposed to stressful circumstances. There is significant overlap at the present time among treatment recommendations for some LUT disorders particularly with regard to ensuring that the patient’s environmental needs are met.

Severe chronic idiopathic LUTS has been described as a naturally occurring model of interstitial cystitis in women. Interstitial cystitis (IC) has been defined as a disease of chronic irritative voiding signs, sterile and cytologically negative urine and cystoscopic observation of submucosal petechial hemorrhages. The same description in which cystoscopy was not performed in cats but in which other appropriate diagnostic procedures did not identify a cause became defined as Feline Interstitial Cystitis (FIC).

In addition to epithelial abnormalities identified in the bladder of cats with FIC, investigators found significant alterations in components of acetylcholine synthesis and release in the esophageal mucosa from cats with FIC. This suggested that changes in the nonneuronal cholinergic system may contribute to alterations in cell-to-cell contacts and possibly communication with underlying cells that may, in turn, contribute to changes in sensory function and visceral hyperalgesia. Differences in sensory neuron anatomy and physiology also are present in cats with FIC suggesting a more widespread abnormality of sensory neuron function. The acoustic startle response is a reflex motor protective response to a perceived threat. It is a brainstem reflex response to unexpected auditory stimuli and is increased in cats with FIC.

Differences in sympathetic nervous system function have also been identified in cats with FIC. Among them are changes in the brain stem in the region associated with the most important source of norepinephrine in cats and humans. It is involved in such brain functions as vigilance, arousal and analgesia and mediates the visceral response to stress. Other changes in brainstem help to explain the waxing and waning course of symptoms and the aggravation of signs by environment stressors.

Some cats with FIC appear to have abnormalities in the hypothalamic-pituitary-adrenal axis such that there is a decrease in serum cortisol secretion compared with healthy cats. Adrenal glands in these cats were grossly smaller in cats with FIC when compared to healthy cats.

Cats with FIC often have variable combinations of comorbid disorders such as behavioral, endocrine, cardiovascular and GI problems. External stressors appear to exacerbate clinical signs of these disorders. Many human beings with IC suffer from variable combinations of comorbid disorders as well. These appear to have no consistent pattern of onset and so cannot be attributed to LUTS but rather may be some common disorder affecting more than one organ which then responds in its own way.

Ongoing research in both humans and cats with chronic LUTS has begun to include a more comprehensive evaluation of the entire patient. Nosology is defined as the classification of diseases. Until a better understanding of the larger picture of cats presenting with LUTS, naming this constellation of symptoms and organs systems involved should remain vague and not reflect only LUTS. Dr. Buffington has suggested “Pandora’s Syndrome” He and his colleagues, Drs. Westropp and Chew propose tentative criteria for diagnosis of Pandora syndrome:

1. Presence of clinical signs referable to other organ systems in addition to chronic idiopathic signs for which the patient is being evaluated
2. Evidence of early adverse experience (e.g. abandonment, orphaning) and which may differ by individual
3. Waxing and waning of severity of clinical signs with events that (presumably) activate the central stress response system
4. Resolution of signs with effective multimodal environmental modification

Whatever the eventual name, restricting the description of these patients to their LUTS does not capture all of the currently recognized features of the syndrome. A more comprehensive evaluation of cats with these and other chronic idiopathic signs may result in a more complete diagnosis and lead to additional treatment approaches that may improve outcomes. For example, the relationship between the environment and health is quadratic rather than linear, with both deficient and threatening environment increasing the risk of poor health outcomes.
Individual patients presenting with chronic LUTS benefit by a more comprehensive evaluation to elucidate the effect on risk for Pandora syndrome. Included in this history should be:

- Where the cat was obtained
- Any other health or behavior problems that may be present
- Structure of the cat’s environment – amount of time indoors, activity level, availability and management of resources, other cats in the home, people living with the cat.
- Presence of signs referable to other organ systems
- Perceived allergic responses to skin, lung or GI tract
- Any unusual or problematic behaviors

The physical exam should be performed with evaluation of the lower urinary tract last to avoid being distracted and missing other abnormalities such as over-grooming, obesity, acne, cardiac abnormalities or GI tract issues.

For an initial episode in an apparently healthy, young unobstructed patient, the most likely explanation is either a sickness behavior in an otherwise healthy cat or acute idiopathic LUTS. After ruling out other causes of LUTS, the client should be counseled regarding individually tailored multimodal environmental modification (MEMO) to make sure the cat’s environmental needs are being met. The client can also be taught to look for other signs of sickness behaviors and to evaluate response to MEMO for adequacy of accommodation.

Table 1
Forms used as part of the evaluation of cats presented the Ohio State University Veterinary Medical Center for evaluation of chronic lower urinary tract signs. These forms have not been formally validated beyond their face validity for cases in the authors’ practice area. They are offered as an example of an instrument that could be developed and validated for broader use.

Cat and client history form
Cat's name_____________________ Owner name_____________________ Date_____________

Contact information: Telephone: ☐__________ E-mail: ☐__________ ☐ Please check preferred method of contact

Cat Information: Breed__________ Color__________ Date of Birth__________ Weight ☐ lb ☐ kg
Owned for? ☐ years ☐ months; ☐ M ☐ F ☐ Neutered? If yes, date: _______ (month/year)
Declawed? ☐ N ☐ Y If yes, Front only ☐ All four paws ☐

Body Condition (please check box that looks most like your cat):

- ☐ Skinny
- ☐ Lean
- ☐ Moderate
- ☐ Stout
- ☐ Obese

Please check the boxes that best apply to your cat:

Diet: (please be as specific as you can, eg, Buckeye Best (company) Adult Chicken and Rice (flavor)
Wet food: name__________________________ ☐ None ☐ 25% ☐ 50% ☐ 75% ☐ 100%
Dry food: name__________________________ ☐ None ☐ 25% ☐ 50% ☐ 75% ☐ 100%

How many hours each day, on average: does your cat spend indoors?
☐ Indoor only ☐ 18-24 ☐ 12-18 ☐ 6-12 ☐ 0-6 Is time outside supervised? ☐ Yes ☐ No

If you have more than one cat, what is their relationship? ☐ Not related
☐ Littermate ☐ Sibling ☐ Parent-Offspring ☐ Other (____________________)
Where did you obtain your cat (source)?
- Shelter
- Offspring from a pet I already own(ed)
- Purchased from a friend
- Gift
- Purchased from a breeder
- Purchased from a pet shop
- Stray/orphan
- Other ____________________________

Does your cat frequently (please check all that apply):
- Try to escape
- Pace at outside doors
- Cry at outside doors
- Hide
- Act fearful
- Act friendly
- Follow owners around the home
- Destroy things when left alone
- Act ‘depressed’ (little interest in feeding, grooming, environment, etc.)

Housing (______):
- Apartment: ☐ studio ☐ 1-2 bedrooms ☐ 3 or more bedrooms,
- Zip Code
- House: ☐ attached/twin duplex ☐ attached, 3 or more units, ☐ single
☐ other ________________

Total Cats_____ Total Dogs_____ Other Pets______________

Other People_____________

Please help us understand what your cat does around the house by placing a check (✓) in the box next to each behavior that best describes how commonly your cat does each of the behaviors described below

<table>
<thead>
<tr>
<th>Does your cat:</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good Bit of the Time</th>
<th>Some of the time</th>
<th>A little bit of the time</th>
<th>None of the Time</th>
<th>Does Not apply</th>
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</thead>
<tbody>
<tr>
<td>Leave household articles (furniture, drapes, clothing, plants, etc.) alone</td>
<td>☐</td>
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<td>Eat small amounts calmly at intervals throughout the day</td>
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<td>Drink small amounts calmly at intervals throughout the day</td>
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<td>Use the litterbox</td>
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<td>Get along with people in the home</td>
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<td>Get along with other pets in the home</td>
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<td>Remain calm when left alone</td>
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<td>Stay relaxed during normal, everyday handling (grooming, petting)</td>
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<td>Calm down quickly if startled or excited</td>
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<td>React calmly to everyday events (telephone or doorbell ringing)</td>
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<td>Play well with people</td>
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<tr>
<td>Play well with other family cats</td>
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<td>Show affection without acting clingy or annoying</td>
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<td>Tolerate confinement in a carrier (including travel)</td>
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<td>Groom entire body calmly</td>
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<td>Use scratching posts</td>
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<tr>
<td>Play with toys</td>
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</tbody>
</table>

Comments; anything else your cat regularly does or does not do that you think might be helpful for us to know about?
**Health history**

The cat’s condition today is ____________________________________________________________

Previous illnesses or surgeries _________________________________________________________

Current medications _________________________________________________________________

**Directions**: For items below, please use the following choices to describe how many times you have seen your pet experience the symptom, adding comments/explanation as appropriate.

<table>
<thead>
<tr>
<th>Score</th>
<th>How often does your cat:</th>
<th>Comments/explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Cough</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Sneeze</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have difficulty breathing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stop eating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomit □food □hair □bile □other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have hairballs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have constipation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Defecate outside the litter box</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Strain to urinate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have frequent attempts to urinate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinate outside the litter box</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have blood in the urine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spray urine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Groom more than cats usually do</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shed more than cats usually do</td>
<td></td>
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<tr>
<td></td>
<td>Scratch him/herself more than cats usually do</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have discharge from eyes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seem fearful</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seem to need a great deal of contact or attention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Destroy things when left alone</td>
<td></td>
</tr>
</tbody>
</table>

Please check any of the following diseases your cat has been diagnosed with:

- [ ] Periodontal (dental) disease
- [ ] Asthma
- [ ] Inflammatory bowel disease
- [ ] Skin disease
- [ ] Allergies
- [ ] Diabetes mellitus
- [ ] Cardiomyopathy (heart problems)
- [ ] Obesity
- [ ] Other

_____________________________________________
Household resource checklist

The following questions ask about your cat’s resources so we can learn more about the environment your cat(s) live in. Please check DK if you don’t know, NA if it does not apply, or Yes or No after each question. If you have more than one cat, please answer for all cats. Resources (food, water, litter and resting areas) for each cat are assumed to be out of (cat) sight of each other, such as around a corner or in another room. If they are in sight of each other, please answer No.

Space

1. Each cat has its own resting area in a convenient location that provides some privacy [□] [□] [□] [□]
2. Resting areas are located such that another animal cannot sneak up on the cat while it rests [□] [□] [□] [□]
3. Resting areas are located away from appliances or air ducts that could come on unexpectedly (machinery) while the cat rests [□] [□] [□] [□]
4. Perches are provided so each cat can look down on its surroundings [□] [□] [□] [□]
5. Each cat can move about freely, explore, climb, stretch, and play if it chooses to [□] [□] [□] [□]
6. Each cat has the opportunity to move to a warmer or cooler area if it chooses to [□] [□] [□] [□]
7. A radio or TV is left playing when the cat is home alone [□] [□] [□] [□]

Food and water

8. Each cat has its own food bowl [□] [□] [□] [□]
9. Each cat has its own water bowl [□] [□] [□] [□]
10. Bowls are located in a convenient location to provide privacy while the cat eats or drinks [□] [□] [□] [□]
11. Bowls are located such that other animals cannot sneak up on the cat while it eats or drinks [□] [□] [□] [□]
12. Bowls are washed regularly (at least weekly) with a mild detergent [□] [□] [□] [□]
13. Bowls are located away from machinery [□] [□] [□] [□]

Litter boxes

14. Each cat has its own box (one box per cat, plus one) [□] [□] [□] [□]
15. Boxes are located in convenient, well-ventilated locations that still give each cat some privacy while using it [□] [□] [□] [□]
16. Boxes are located on more than one level in multi-level houses [□] [□] [□] [□]
17. Boxes are located so another animal cannot sneak up on the cat during use [□] [□] [□] [□]
18. Boxes are located away from machinery that could come on unexpectedly during use [□] [□] [□] [□]
19. The litter is scooped daily [□] [□] [□] [□]
20. The litter is completely replaced weekly [□] [□] [□] [□]
21. Boxes are washed regularly (at least monthly) with a mild detergent (like dishwashing liquid), rather than strongly scented cleaners [□] [□] [□] [□]

Litter boxes (continued)

22. Unscented clumping litter is used [□] [□] [□] [□]
23. A different brand or type of litter is purchased infrequently (less than monthly) [□] [□] [□] [□]
24. If a different type of litter is provided, it is put in a separate box so the cat can choose to use it (or not) if it wants to [□] [□] [□] [□]

Social contact

25. Each cat has the opportunity to play with other animals or the owner if it chooses to on a daily basis [□] [□] [□] [□]
26. Each cat has the option to disengage from other animals or people in the household at all times [□] [□] [□] [□]
27. Do any cats interact with outdoor cats through windows? [□] [□] [□] [□]

Body care and activity

28. Horizontal scratching posts are provided [□] [□] [□] [□]
29. Vertical scratching posts are provided [□] [□] [□] [□]
30. Chew items (e.g., cat-safe grasses) are provided [□] [□] [□] [□]
31. Toys to chase that mimic quickly moving prey are provided [□] [□] [□] [□]
32. Toys that can be picked up, carried, and tossed in the air are provided [□] [□] [□] [□]
33. Toys are rotated on a regular basis (at least weekly) to provide novelty [□] [□] [□] [□]

If you have additional comments on any of the questions, please write them below, including the question #.

By submitting this form, you agree that anonymous information from it may be used for cat health-related research.
The interrelationship between calcium, phosphorus, parathyroid hormone, activated vitamin D and fibroblast growth factor has a profound impact on the progression of chronic kidney disease (CKD) in dogs and cats. Beneficial effects of calcitriol treatment during CKD have traditionally been attributed to regulation of parathyroid hormone (PTH). New analysis of information emphasize direct renoprotective actions independent of PTH and calcium. It is now apparent that calcitriol exerts an important effect on renal tubular Vitamin D which may be important in maintaining adequate circulating Vitamin D. This in turn may be vital for important actions of Vitamin D on peripheral tissue. Limited information is available reporting the benefit of calcitriol treatment in dogs and cats with CKD. However, a survival benefit has been shown in dogs with CKD treated with calcitriol compared to placebo. The concentrations of circulating Vitamin D have recently been shown to be low in people and dogs with CKD and are related to survival in people. In 2015, there will be compelling data regarding the benefit of calcitriol use in cats with CKD.

Rather than focus on the dearth of evidence for several forms of intervention, this talk will focus on a historic review of the use of dietary therapy, phosphorus binding agents and calcitriol over a ten year period. These are all client-owner cats. Therefore, these are not randomized, blinded, controlled studies. Rather, these cases are a demonstration of practical interventions that have prolonged good quality of life in cats who may not have agreed to all of the recommendations made in the literature.

In assessing renal disease in cats, the most sensitive indicator is the loss of urine concentrating ability. The use of an early morning urine sample to assess urine specific gravity (USG) may help to counter effects of diet or drugs on a tested sample. Using the International Renal Interest Society (IRIS) values for classification of renal disease can be helpful in planning therapy. In some classifications IRIS 2 is divided into 2a (Cr. 1.6-2.4 mg/dl) and 2b (2.5-2.8 mg/dl). In our practices the classification of 2a with USG less than 1.030 eating a mostly dry diet formula, for example, are started on treatment for chronic progressive renal disease (CPRD). Early intervention prolongs quality of life, good body condition score and wellbeing in a number of key ways. We use ultrasound guided cystocentesis in every cat from whom urine is obtained. This allows a quick early morning visit by the owner, a sterile sample for culture if indicated, a full assessment of the appearance of the urinary bladder and observation of complications such as uroliths.

One of the most frustrating aspects of treating this and any condition requiring lifelong therapy in cats is the difficulty clients have complying with our recommendations. Cats resist contact or intervention they haven’t agreed to and clients want to preserve the relationship they have with their cat, often at the expense of appropriate therapy. It is essential then to choose the most effective forms of therapy, to provide options when resistance is experienced and to communicate a willingness to the client to assist in preserving the relationship they have with their beloved cat.

While it has been shown that dietary modification has the most positive long-term effect on outcome, the relationship between survival and protein restriction or the attendant restriction of phosphorus has yet to be illuminated fully. Strong evidence, however, supports dietary phosphorus restriction in animals with kidney disease. Serum phosphorus is an independent predictor of disease in cats with chronic kidney disease. Cats with induced renal disease fed phosphorus-restricted diets had less severe histological renal changes than cats fed normal diets.

Phosphate retention and hyperphosphatemia are primarily due to impaired renal phosphate excretion. If renal function is normal, clinically significant hyperphosphatemia seldom develops. In the early stages of CPRD increased levels of PTH can keep serum phosphorus within the reference range by decreasing expression of the sodium-phosphate transport system in the proximal tubule resulting in increased urine phosphate excretion. This allows for normalization of serum phosphorus at the expense of hyperparathyroidism.

As cats are quite specific about preferences in taste, texture and flavor, the use of renal formulated diets may not always be possible. Alternatives may not have been thoroughly tested to the extent that prescription diets are but the truth of the statement “It is more important THAN he eats than WHAT he eats” is undeniable. Treatment goals of dietary modification start with maintaining body weight and a normal body condition score. If renal diets are not tolerated, warm canned diets diluted with some form of flavored moisture are a good choice. Other alternatives include adding other forms of moisture to food to increase fluid intake, providing flavored waters to encourage moisture consumption, water fountains and multiple drinking places throughout the house.

If a renal diet is not fed, most cats will tolerate low doses of aluminum hydroxide in food to act as a phosphorus binder, before serum phosphorus levels leave the normal range. Serum phosphorus should remain in the 4-5 mg/dl range, especially if calcitriol is considered. Low body condition scores and malnutrition are negative prognostic indicators in dogs and the same is likely to be true in cats. If adequate caloric intake and preservation of lean body mass does not occur, quality of life will decline.

Studies done to confirm preservation of lean body mass in cats fed a low protein diet, about 28% on an as-fed basis, were, as one would anticipate, time restricted to around 4 months. With the advent of a better plan for managing renal patients, they are living for
years with stable renal values and hematocrits within the normal range. The effects of protein restriction on the body condition scores of cats with CPRD should be evaluated. Until then, we all have observed the protein cachexia of our renal patients. It is crucial to preserve adequate caloric intake and adequate protein for these patients.

The effects of uremia on appetite are well known, particularly in human renal patients. The use of H2 blockers for uremic gastritis can be helpful in encouraging consumption of adequate calories. The use of mirtazapine as an appetite stimulant is helpful in those cats who can tolerate it. We use 1/8 of a 15 mg tablet every day to every third day depending upon response to therapy. Many cats with CPRD are underweight and dosing of ¼ of a tablet as has been recommended is often followed by restlessness, anxiety and vocalizing in cats who are sensitive to it. Clients can be quite upset by this and may be less inclined to follow other treatment recommendations. Both of these forms of therapy imply being able to accomplish giving fragments of a pill to a cat on a regular basis and over a prolonged period of time. Strategies for this should be included in client education including the use of “sticky” high value food like cheese in a can, cream cheese or pill pockets and other soft treats.

Calcitriol has long been reported to provide benefits to the human uremic patient by lowering parathyroid hormone concentration. This has also been reported in dogs and cats. Oral calcitriol has been shown to increase survival in human patients with CPRD including those treated prior to dialysis. The antiproteinuria effects of Vitamin D analogs are of crucial significance because proteinuria is a major risk factor for the progressive decline of renal function in both dogs and cats. Podocytes are critically important in overall glomerular function and structure. Injury to podocytes commonly leads to proteinuria and glomerulosclerosis. A marker for podocyte injury, desmin, was lowered by calcitriol in one model of CPRD in rats. Fibrosis as either glomerulosclerosis or tubulointerstitial fibrosis is a common sequela in CPRD. Calcitriol in physiologic doses interfered with glomerular proliferation and growth, lessening glomerulosclerosis in a rat model. Calcitriol treatment of an experimental glomerulonephritis model in rats inhibited medangial cell proliferation, glomerulosclerosis and albuminuria.

The renin-angiotensin-aldosterone system (RAAS) is a major mediator of progressive renal injury in CPRD. The RAAS system is present entirely within the kidney and is present in most renal cells including tubular epithelia.

Calcitriol is a negative endocrine regulator of RAAS. Calcitriol suppresses renin biosynthesis and has a protective role against hyperglycemia-induced renal injury in diabetic human patients. Through its effect to inhibit RAAS, calcitriol decreases production of Angiotensin II and thus lessens these fibrogenic consequences as well as other harmful renal effects.

A glomerular mesangial or interstitial inflammatory reaction with marked involvement of macrophages and lymphocytes attends all forms of renal disease. Together with control of RAAS, the ability of calcitriol to control inflammation are hallmarks of renoprotective actions.

In our practices, early diagnosis of CPRD at the IRIS 2a or b level is the key to successful management. A cat with or without proteinuria, with or without hypertension with a USG less than 1.030 and normal Calcium and Phosphorus will be started on Calcitriol at a dose of 2.5-3.5 ng/Kg per day. This is compounded into a chicken or fish flavored oil base by a compounding pharmacy licensed to produce compounded pharmaceuticals for the human market. Calcium, Phosphorus and their product will be measured in 2 weeks.

While the literature is clear that iCA is a far more accurate measure of total body calcium, it is an expensive test. Our protocol calls for frequent testing of renal values including calcium and phosphorus. We would be treating a fraction of the cats we can help if this costly test were included. Instead we use a protocol advocated by Larry Nagode and Dennis Chew, Pathology and Urology professors respectively at the Ohio State University Veterinary College.

One of the benefits of the preservation of renal tissue using this protocol is the preservation of erythropoietin production and the consequent preservation of normal hematocrits. Cats with IRIS Stage 3-4 CPRD are still feeling better, more active and eating better with adequate circulating red cells. Anemia is a quality of life issue.

Hepcidin excess prevents iron absorption from the diet and blocks iron release from body stores by binding to and inducing the degradation of the iron export protein ferroportin. A mechanism for the EPO sparing effects of vitamin D is suggested by recent data demonstrating a hepcidin lowering effect of vitamin D. In vitro treatment with vitamin D of monocytes isolated from hemodialysis patients downregulated hepcidin transcription. Furthermore, oral administration of vitamin D in healthy volunteers lowered serum levels of hepcidin by 50% compared to baseline levels within 24 hr and persisted for 72 hr. Supplementation with vitamin D has also been reported to have beneficial effects on increasing erythropoiesis and decreasing inflammation. These initial results are promising, and a randomized controlled study is warranted to determine whether correction of vitamin D deficiency can ameliorate ACD.

References
Journal of Veterinary Emergency and Critical Care, Calcitrol, Calcidiol, Parathyroid hormone and fibroblast growth factor-23 interactions in chronic kidney disease. Volume 23 (2) 2013, pp 134-162.
Pancreatitis is an inflammatory disease of the exocrine pancreas. It can be divided into acute and chronic types based upon histological findings. Two main forms have ben described. Neutrophilic inflammation and varying amounts of pancreatic acinar cell and peripancreatic fat necrosis characterize acute pancreatitis. Chronic pancreatitis is characterized by lymphocytic inflammation, fibrosis and acinar atrophy. While the cell types involved differ in this description, they appear to represent, in some studies, different points on a continuum of disease.

Diagnosis of both forms is difficult. There may be comorbidities that complicate signs. Clinical signs may be vague or mild. The diagnostic tools like imaging or clinical tests can lack sensitivity and specificity. Biopsy samples may be difficult to interpret or unavailable for many reasons.

There appears to be a strong association in several studies between pancreatitis, inflammatory bowel disease (IBD) and cholangitis, giving rise to the term “triaditis”. This may be partially explained by the proximity of the common bile duct and major pancreatic duct in the duodenal papilla. Enteric bacteria were found in >1/3 of cases supporting the suspicion of a relationship between pancreatitis and the translocation of bacteria from the gut. Vomiting, a common sign in cats with IBD or cholangitis may also raise intraluminal pressure and further increase the risk of pancreaticobiliary reflux. The relationship between cholangitis and pancreatitis has recently been challenged however, though its relationship with IBD has not.

Ischemia is another recognized cause of acute pancreatitis. Inadvertent compression or ligature and hypotension during surgery can cause ischemia of the pancreas. Careful surgical technique and anesthetic monitoring prevent these events from occurring. The pancreas can be the cause of ischemia if fibrosis, edema or inflammation compromise pancreatic blood flow. Other causes like infectious agents, hypercalcemia, drug reactions and nutritional imbalances have been reported but are rare. Most commonly pancreatitis is considered idiopathic as no obvious cause can be found.

Serum feline pancreatic lipase immunoreactivity (fPLI) is the most recent addition to laboratory tests seeking a useful diagnostic ante-mortem test for feline pancreatitis. There are two tests, developed by the same laboratory. SpecfPLI is a quantitative test for which concentrations > 5.3 are consistent with pancreatitis. A grey zone is found from 3.5-5.3ug/l and is notable on the Spec test and on the Snap fPLI test, which is a semi-quantitative test. A positive Snap fPLI includes the grey zone when it is positive so results should be confirmed by Spec fPLI. The sensitivity of the Spec fPLI is still without adequate data. Moderate to severe pancreatitis was 100% sensitive in one study but much lower, 54%, for mild pancreatitis based upon histopathology. However, the number of patients was small and there was some bias evident on patient selection for histopathology. More studies are needed to properly evaluate sensitivity and specificity of SpecfPLI. Snap fPLI has not been independently validated. Importantly, fibrosis or atrophy from long-standing chronic pancreatitis would not be expected to increase fPLI.

Other abnormal laboratory findings have been observed but are not diagnostic as well. From 26-55% of cats have a normocytic, normochromic nonregenerative or regenerative anemia. Less than half have a leukocytosis. Leukopenia may be present and has a poorer prognosis. Other hematological findings are non-specific and cannot distinguish between acute, chronic or suppurative pancreatitis. Biochemistry abnormal values are often present but are not specific for pancreatitis and may represent comorbid conditions with pancreatitis.

Abdominal radiographs are may be suggestive of cranial loss of serosal detail or a mass effect but are largely useful to rule out concomitant conditions like intestinal obstruction. Ultrasound is relatively specific in differentiating pancreatitis from other GI disease but cannot differentiate between acute and chronic forms. Hypoechoic pancreas, hyperechoic peripancreatic adipose or abdominal effusion is relatively specific for pancreatitis in cats. Mild forms of pancreatitis are more difficult to discern than moderate to severe forms on ultrasound. In some cats, the pancreas is more difficult to detect and is dependent on operator experience.

The use of endosonography may improve the general visualization but did not alter the diagnosis of pancreatitis in one study. Ultrasound is still recommended for diagnosis of pancreatitis and will reveal other abnormal findings such as pancreatic masses, cysts or stones. Computed tomography has not been helpful and is not recommended for diagnosis. Magnetic resonance imaging is the modality of choice in humans and may be helpful in cats.

Histopathology remains the gold standard for ante-mortem diagnosis though there are limitations to this as well. Cats with severe pancreatitis are poor candidates for anesthesia. Even for those patients stable enough, the results may not alter treatment planning and patient management. Patients undergoing laparotomy or laparoscopy for other reasons should have the pancreas biopsied. Focal lesions may be visible as well as more generalized changes that will guide sample collection. Multiple samples are recommended as lesions can be geographically distributed or very mild and difficult to discern. Mild changes may not explain the patient’s clinical signs as well.

Acute and Chronic Pancreatitis: What to do?
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425
Despite the challenges of diagnosis, pancreatitis is an important condition. Anorexia and weight loss found with pancreatitis can cause concurrent hepatic lipidosis. Several studies have shown the relationship between Diabetes Mellitus (DM) and pancreatitis. Other concurrent diseases can be complicated by the presence of pancreatic inflammation most notably IBD. End-stage CP can result in exocrine pancreatic insufficiency.

Management of pancreatitis is comprised of three main aspects: nutrition and antiemetic therapy, fluid and electrolyte correction and analgesia. A high protein, low carbohydrate, moderate fat diet is the recommended formulation. While fasting is not recommended, gradual reintroduction of food should be instituted to avoid the electrolyte and other disturbances that occur with refeeding syndrome. Though nausea may be difficult to discern, it should be treated to insure adequate intake of food. NK-1 receptor antagonist maropitant and 5HT3 antagonists are beneficial. Maropitant may also relieve some of the pain associated with pancreatitis. Cobalamin deficiency is common in cats and should be addressed with B12 injections weekly for 6 weeks and every 1-2 months thereafter. Appetite improvements with the use of cobalamin supplementation have been reported.

If voluntary food intake is not rapidly restored a nasoesophageal tube for short-term use or an esophagostomy or gastrostomy tube may be required. The goal of a nasoesophageal tube is for stabilization until anesthetic risk is lowered adequately to permit a more lasting tube to be placed. In the case of severe malnutrition and persistent anorexia, partial parental nutrition along with some enteral nutrition has been shown to maintain gut wall barrier function in humans.

Vomiting, anorexia and diarrhea can lead to severe dehydration and electrolyte disturbances. Hypokalemia and hypocalcemia are uncommon. Aggressive fluid therapy is required to correct pancreatic hypoperfusion.

If pain is a common feature of pancreatitis though difficult to evaluate in cats. Buprenorphine, oxymorphone or fentanyl may be good choices. Comorbidities must be treated at the same time, insulin for DM, therapy for diabetic ketoacidosis, cholangitis or inflammatory bowel disease. Plasma (20ml/kg i.v.) or colloids (10-20ml/kg/day i.v.). may be indicated in the presence of hypoproteinemia or shock. Colloids such as dextran 70 and hetastarch may also have antithrombotic effects that help maintain the microcirculation.

Prophylactic broad-spectrum antibiotics (e.g. amoxicillin ± enrofloxacin depending on severity) may be warranted in patients with shock, fever, diabetes mellitus or evidence of breakdown of the GI barrier. Bacterial translocation has been demonstrated in experimental feline pancreatitis using distinct E.coli placed in the colon, and other sites e.g. bile, and colonization was prevented with cefotaxime (50mg/kg TID). A recent study revealed that bacterial infection is present in the pancreas of 35% (11/31) of cats with moderate to severe pancreatitis. The high frequency of infection (71%, 5/7) in acute necrotizing and suppurative pancreatitis may be linked to the poor prognosis associated with this form of pancreatitis. These localization and type of intrapancreatic bacteria suggests translocation of enteric bacteria is a likely source of infection.

Coagulation abnormalities should be pursued and treatment with parenteral vitamin K can be assessed. Where a coagulopathy e.g. DIC, or hypoproteinemia are present, or the patient with pancreatitis is deteriorating, fresh frozen plasma (10-20 ml/kg) may be beneficial in alleviating the coagulopathy, hypoproteinemia and restoring a more normal protease-antiprotease balance. The administration of heparin (75-150 IU/kg TID) may be potentially useful in ameliorating DIC, promoting adequate microcirculation in the pancreas and clearing lipemic serum. In experimental pancreatitis isovolemic rehydration with dextran has also been shown to promote pancreatic microcirculation in dogs. A dopamine infusion (5μg/kg/min) had a protective effect when administered to cats within 12 hrs. of induction of experimental pancreatitis. H1 and H2- antagonists blocked the progression of edematous to hemorrhagic pancreatitis in experimental cats and may be beneficial in patients.

Oral pancreatic enzyme extracts have been reported to reduce pain in humans with chronic pancreatitis, though this is controversial. The presence of a protease mediated negative feedback system has not been described in cats.