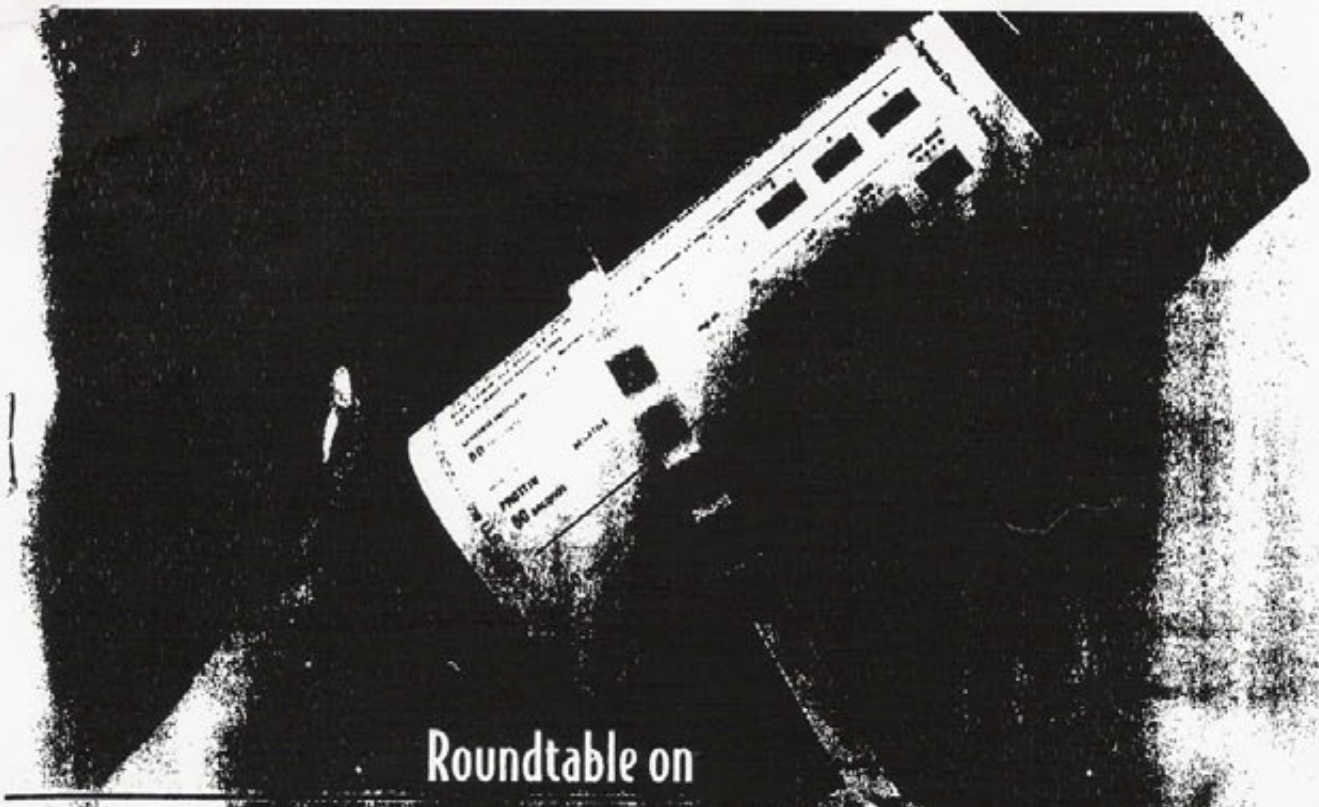

Roundtable on IDIOPATHIC CYSTITIS in Cats: What's New in 2002

Feline lower urinary tract diseases (LUTDs) are a heterogeneous group of disorders that may result from fundamentally different causes. Although many single or multiple interacting causes of nonobstructive hematuria, dysuria, pollakiuria, crystalluria, and periuria have been identified in cats affected with LUTD, the exact cause remains unknown in a substantial number of patients. During the past two decades, our knowledge of specific causes and the associated natural course of several types of LUTD have resulted in advances in their diagnosis and specific treatment. However, consistently effective treatment and prevention of idiopathic forms of cystitis remain an elusive goal.

On November 10, 2001, a panel of veterinarians met to share their collective experiences on the diagnosis and treatment of idiopathic cystitis. In Part 1 (March 2002) of this two-part roundtable, the panel clarified terminology and advocated use of a defined database as a practical diagnostic strategy. Part 2 examines alternative treatment approaches.

The Biologic Behavior of Idiopathic Cystitis

Carl A. Osborne, D.V.M., Ph.D.: In order to formulate a meaningful prognosis for cats with idiopathic cystitis and evaluate the benefits and risks associated with various types of therapy, we should consider the biologic behavior of the disorder. In your experience, what is the natural course of idiopathic cystitis in untreated cats?

John Kruger, D.V.M., Ph.D.: In many instances, acute idiopathic cystitis is self-limiting and signs resolve without treatment. Signs might recur after a variable period of time and again resolve without treatment. Some cats have more chronic or frequently recurring signs. However, even in this subset of cats, spontaneous remis-

This roundtable is made possible by an educational grant from Nutramax Laboratories®.

sion of signs may occur. An unpublished study recently conducted at Michigan State University College of Veterinary Medicine, East Lansing, involved cats with untreated acute idiopathic cystitis. In about 60 percent of the cats, clinical signs resolved completely within one week without intervention. However, about 50 percent of these cats experienced recurrence of clinical signs within two years. Although the biologic behavior of idiopathic cystitis is unpredictable, it is my impression that a majority of cats have the self-limiting form of the disease and may or may not have recurrent episodes.

Theresa Cranny, D.V.M.: Although the condition itself is not life-threatening, its recurrent nature demands considerable patience of an owner. Long-term interventions are often necessary.

Paul Welch, D.V.M.: Many cats have one acute episode and never return to the clinic. Unfortunately, a high number of cats return repeatedly, and veterinarians should prepare clients for this scenario. Many women are familiar with human interstitial cystitis and thus, when veterinarians explain the concept of idiopathic cystitis, the female client tends to grasp the reality and possibility of chronicity quite well.

Osborne: Our experience at the University of Minnesota College of Veterinary Medicine, Saint Paul, is similar to that observed at Michigan State. In most cats with idiopathic cystitis, clinical signs apparently subside in three to 10 days. That is the good news. The bad news is that these signs often recur unpredictably. In your experience, what is the average duration of clinical signs in cats with recurrent episodes of idiopathic cystitis?

Kruger: In general, the duration of signs is approximately five to 10 days in cats experiencing the initial episode of acute idiopathic cystitis. In a series of eight untreated cats with acute nonobstructive idiopathic cystitis, pollakiuria and hematuria resolved completely in an average of six days (range: three to 10). Interestingly, our observations suggest that the frequency and severity of episodes decrease with age. Some cats eventually stop experiencing recurrent episodes of signs. Thus, the risk of recurrence of signs appears to diminish over time.

Marcia Levine, D.V.M.: The frequency and duration of signs are markedly variable, and thus we caution owners that idiopathic cystitis tends to be recurrent in nature and not likely to resolve completely.

Osborne: The frequency of recurrence of idiopathic cystitis often declines as the cat ages—to the point where, without therapy, the cat may remain asymptomatic. One of the differences between interstitial cystitis in humans and in cats is that the human disorder often becomes progressively more severe. In cats, however, acute recurrent episodes tend to be more common than a chronic progressive course. How should this difference influence our evaluation of the effectiveness of various forms of therapy?

Kruger: There is a tendency to study cats with the more chronic forms of the disease. Because of the frustration and expense associated with managing cats with chronic idiopathic disease, they are often referred to research centers and are easily recruited into studies. On the other hand, cats with more acute self-limiting forms of the disease are difficult to study. They are seldom referred to a university, and owners are often reluctant to enroll their cat in a study if they know that the pet's problem will probably resolve spontaneously in a relatively short period.

Osborne: Because clinical signs of idiopathic cystitis are frequently self-limiting and short in duration, considerable debate exists about the efficacy of various types of therapy advocated for this →

Our Participants

Theresa Cranny, D.V.M., is an associate veterinarian, Lincolnway Animal Hospital, Matteson, Illinois.

John Kruger, D.V.M., Ph.D., Dipl. A.C.V.I.M., is an associate professor in the Department of Small Animal Clinical Sciences, Michigan State University College of Veterinary Medicine, East Lansing.

Marcia Levine, D.V.M., is owner of Summer Street Animal Hospital, New York.

Carl A. Osborne, D.V.M., J.D., Ph.D., Dipl. A.C.V.I.M. (Moderator) is professor of the Department of Small Animal Clinical Sciences, University of Minnesota College of Veterinary Medicine, Saint Paul.

Paul Welch, D.V.M., is owner of Forest Trails Animal Hospital, Tulsa, Oklahoma.

DR. JOHN KRUGER

The clinical features and biologic behavior of idiopathic cystitis could be viral in nature.

disorder. Why? Because any form of therapy might appear to be beneficial as long as it is not harmful. The self-limiting nature of some forms of idiopathic cystitis underscores the need for controlled, prospective, double-blind studies to determine objectively the value of various forms of therapy. Let me emphasize one additional caveat about recurrent disease. Not all recurrences are identical in terms of cause. The same clinical signs may recur in cats but have an entirely different cause. As mentioned in Part 1 of this roundtable (March 2002), appropriate diagnostic evaluation also applies to cats with recurrent signs of urinary tract disease.

Welch: A recent study published in the *Journal of Urology* reported that in a group of 581 women, 183 different types of therapy were tried. After reading this report, I could better grasp or put into perspective how frustrating it has become to unravel the mystery of idiopathic cystitis. I believe that considerable research is required to find the cause or causes—much less the best treatment—of cystitis in cats.

SEARCHING FOR THE CAUSATIVE LINKS

Osborne: In light of the biologic behavior of idiopathic cystitis in many cats and our inability to identify causative agents by conventional diagnostic tests, what is your opinion about the hypothesis that viruses may be involved in some cases?

Kruger: In human medicine, several viruses have been associated with hemorrhagic cystitis. Since the clinical features and biologic behavior of idiopathic cystitis could be consistent with a viral urinary tract infection, it is tempting to speculate that viruses could also play a role in some cases of idiopathic cystitis. In fact, the role of viruses in the etiopathogenesis of idiopathic cystitis has been studied for over 30 years. In 1969, a feline calicivirus was isolated from a male Manx cat with obstruction. Although initial experimental studies of the Manx calicivirus were encouraging, the virus theory fell into disfavor because of the inability of other researchers to isolate viruses from urine obtained from cats with lower urinary tract disease. However, there is increasing evidence that feline calicivirus urinary tract infections may be more common than previously believed. We recently isolated two feline caliciviruses in urine obtained from cats with idiopathic cystitis. Although isolation does not establish cause, it certainly suggests that we need to reexamine the causative role of caliciviruses in idiopathic cystitis.

Osborne: We also have identified virus particles with ultrastructural characteristics of caliciviruses in urethral plugs removed from male cats with lower urinary tract disease.

Levine: In addition to a viral link, researchers may find a dietary connection to idiopathic cystitis—either a deficiency in the building blocks necessary for proper formation of the protective glycosaminoglycan layer or some metabolic or dietary by-product that disrupts this layer.

WHAT IS THE ROLE OF GLYCOSAMINOGLYCANS?

Osborne: The luminal surface of the urinary tract is normally covered by a protective barrier called the "glycosaminoglycan layer" (see box, "The Importance of Glycosaminoglycans to the Urinary Tract"). Glycosaminoglycans are negatively charged and avidly bind water molecules so that they minimize the movement of many constituents found in urine through the epitheli-

The Importance of Glycosaminoglycans to the Urinary Tract

Glycosaminoglycans (GAGs) are large molecular structures composed of alternating sequences of two basic types of carbohydrates: an amino sugar and an acidic sugar. An amino sugar is a glucose molecule with a nitrogen grouping ($-NH_2$) attached to a carbon atom of the glucose structure. All GAGs, with the exception of hyaluronan, are attached to a core protein, forming a proteoglycan complex. These complexes carry a strong negative charge that attracts and holds large quantities of water. The proteoglycan structures are found on the surface of cells that line the urinary tract, creating a water barrier that protects the cells from urine solutes, as well as from bacterial and crystal adherence.

DR. CARL OSBORNE

Preliminary data suggest that glycosaminoglycans may be altered in cats with idiopathic cystitis.

um into the deeper layers of the bladder wall. Studies in humans with interstitial cystitis suggest that damage to this protective layer may be involved in the pathogenesis of this disease. As a result, it is logical to ask whether a similar phenomenon may be occurring in cats with idiopathic cystitis. What is your opinion?

Kruger: Although alterations may occur in the glycosaminoglycan or epithelial layer in the bladder of cats with naturally occurring disease, the problem is determining whether the alterations are causing the disease or are the result of another pathologic process. Viruses could potentially affect the glycosaminoglycan layer, transitional epithelium, or other layers in the bladder.

Regardless, glycosaminoglycans apparently play an important role in preventing adherence of microorganisms as well as limiting transepithelial movement of urine proteins and other solutes. Therefore, alterations in the glycosaminoglycan layer play a potential role in the development and control of idiopathic cystitis.

Osborne: Some preliminary data suggest that glycosaminoglycans may be altered in cats with idiopathic cystitis. There is also evidence that bladder mucosal permeability defects, or so-called "leaky bladders," may occur in some cats with idiopathic cystitis. Although a cause-and-effect relationship has not been established, of what possible significance are these observations?

Kruger: There are several possible scenarios. First, if this layer is altered within the bladder urothelium, the underlying tissues could be exposed to noxious urine constituents that cause an abnormal sensory stimulation resulting in urgency and discomfort. So-called "neurogenic inflammation" from stimulation of specific types of sensory nerve fibers can be pro-inflammatory and serve to become self-perpetuating. Another theory is that these urine constituents could potentially activate other cellular components of the bladder wall, specifically, the mast cells, which can set up an inflammatory response.

Welch: The scenario is similar to what occurs in humans with stomach ulcers. When the stomach lining is damaged or defective, the result is a burning sensation, along with pain and discomfort.

Levine: Because urine is caustic, it would intuitively make sense that any organ storing urine needs an intact protective layer to prevent urine damage to underlying tissues.

Osborne: In theory, how might viral infections be related to altered glycosaminoglycans?

Kruger: Certain viruses, such as calicivirus, tend to infect epithelium. Arguably, viral injury caused to host tissues could involve a number of mechanisms, but one of them can certainly be direct cytotoxic damage to cells. Another could be virus-induced alterations in cellular functions and expression of proteins. Synthesis of proteins can be altered, resulting in increased or decreased protein production or changes in protein composition. Thus, a number of mechanisms may be involved in viral injury to the urothelium.

EXAMINING THERAPEUTIC OPTIONS

Osborne: Based on our current knowledge of idiopathic cystitis and keeping in mind that it may have more than one cause, what types of supportive and symptomatic therapy do you recommend to your clients?

Kruger: Clients need to understand that, because we cannot identify a single causative factor, empirical or symptomatic therapy may be the only alternative. In cats with chronic disease, different types of therapy may be tried to determine what might work for an individual cat, including intermittent pain management and initiation of amitriptyline or glycosaminoglycan-replacement therapy. In addition, environmental factors often play an important role in cats with chronic cystitis.

Cranny: Therapy often requires multimodal intervention that includes decreasing stress, providing an adequate number of litter boxes, increasing water intake, and initiating glycosaminoglycan supplementation.

Levine: We may find dietary manipulation or supplementation helpful in managing idiopathic cystitis. When we artificially create diets for cats, we risk the inadvertent omission of an essential nutrient, as we learned from the taurine-cardiomyopathy link. Although a "ground-rat"→

diet is not practical or socially acceptable, we may find that more closely replicating a more natural feline diet could eliminate certain feline diseases.

DR. THERESA CRANNY

While stress is rarely the cause of any disease, cats experiencing stress have a higher incidence of recurrent idiopathic cystitis.

What Dietary Modifications Should Be Considered?

Osborne: Assuming we are not talking about urolithiasis, is any form of dietary modification likely to be helpful in cats with idiopathic cystitis?

Levine: Cats fed canned diets usually have a greater total water intake than that of cats consuming dry diets.

Osborne: What is the advantage of increasing urine volume by encouraging water intake?

Levine: Additional fluid intake makes the urine more dilute and thus less irritating to the bladder wall, especially if the protective glycosaminoglycan layer is disrupted. In addition, increased fluid intake has been shown to decrease stone formation.

Cranny: Naturally, some cats resist a change in diet from dry to canned foods. If that resistance becomes a factor, owners can encourage increased water consumption by adding flavorings to tap water or installing a running water fountain, which often is well-received by cats. The goal is to increase urine volume and decrease urine concentration in order to dilute and promote excretion of irritants.

Levine: Gradual transition to a high-quality canned diet usually works, as some cats reject abrupt changes.

Does Environmental Stress Play a Role?

Osborne: What other management strategies would you consider?

Cranny: While stress is rarely the cause of any disease, anecdotally, there is a higher incidence of recurrence in cats experiencing stress. Owners therefore should be encouraged to try to determine which environmental conditions may be causing stress and eliminate them accordingly.

Welch: Introducing a new food product in itself could represent a stressful incidence, so owners need to be cautious when introducing foods previously unfamiliar to the cat.

Kruger: On the other hand, there is little evidence supporting the idea that stress is a primary cause of idiopathic cystitis. However, changes in the household seem to precipitate episodes, and stress may aggravate clinical signs. Thus, I believe that stress is associated with clinical signs of idiopathic cystitis, even though it may not be a primary factor.

Are Glucocorticoids and Other Anti-inflammatory Agents Beneficial?

Osborne: Glucocorticoids have been recommended by some clinicians to minimize signs associated with

The Efficacy of Chondroitin Sulfate in Treating Interstitial Cystitis[a]

By G. Steinhoff, B. Ittah, and S. Rowan, Department of Urology, Capital Health Region, Victoria, B.C., Canada

OBJECTIVE: An open label study of chondroitin sulfate was undertaken to determine the response of patients with interstitial cystitis and positive potassium test results to this agent.

METHOD: Eighteen patients with class features of interstitial cystitis were enrolled in the study. Patients received 40 mL chondroitin sulfate 0.2 percent instilled intravesically once a week for four weeks and then once a month for 12 months. At the same time, Quality of Life Improvement scores, voiding diaries, and pain and voiding indexes were reviewed.

RESULTS: Thirteen of 18 patients were followed for the entire 13-month study. Twelve of these patients responded to treatment within three to 12 weeks, on average. A total of six of 13, or 46.2 percent, showed good response; two of 13, or 15.4 percent had a fair response; four of 13, or 30.8 percent, had a partial response; and one of 13, or 7.7 percent, showed no response.

CONCLUSION: Intravesical chondroitin sulfate seems to demonstrate some beneficial effects in the treatment of interstitial cystitis patients with positive potassium stimulation test results.

[a]From *Can J Urol.* 2002;Feb:1454-8.

DR. MARCIA LEVINE

When I initially heard the theory behind glucosamine-chondroitin therapy, I thought it made sense.

inflammation. However, in a double-blind placebo-controlled study of idiopathic cystitis conducted at the University of Minnesota, there were no differences in responses detected between the steroid-treated and placebo groups. In both groups, dysuria and hematuria subsided within one week. Dr. Kruger, will you summarize what is known about the other types of therapy used to treat this disorder?

Kruger: During the past three decades, more than 30 therapies have been recommended for treating idiopathic cystitis, including amitriptyline, hydroxyzine, butorphanol, dimethylsulfoxide, and many others. Few of these agents have been evaluated in controlled studies. Hydroxyzine is an antihistamine. Amitriptyline also has some potent antihistamine effects, along with potent anticholinergic and analgesic properties. I have not used dimethylsulfoxide. This agent has been used to treat interstitial cystitis in humans, but limited studies have shown it to have potential adverse effects in cats.

Regarding amitriptyline, a controlled study of short-term amitriptyline therapy in cats with acute nonobstructive idiopathic cystitis yielded some interesting findings. First, there was no difference between amitriptyline and the placebo in terms of reducing the frequency of urination or resolution of hematuria. Three cats developed urinary tract infections after administration of amitriptyline. In addition, cats treated with amitriptyline were more likely to have recurrent signs that occurred sooner and were of longer duration. However, these results do not preclude the possibility that long-term amitriptyline treatment may be beneficial in cats with chronic or frequently recurrent forms of idiopathic cystitis.

What About Glycosaminoglycans?

Osborne: Recently, there has been considerable interest in the cytoprotective glycosaminoglycan layer lining the mucosal surface of the urinary tract. Randomized, double-blind clinical studies of the efficacy of one glycosaminoglycan therapy—pentosan polysulfate—in humans with interstitial cystitis revealed reduction in the severity of symptoms in a significant number of patients. Although results of controlled clinical trials are not available, do any of you have empirical experience with glycosaminoglycan therapy in cats with idiopathic cystitis? ➔

DR. PAUL WELCH

The goal is to find a long-term beneficial treatment by exploring further the various treatment agents.

Welch: For initial episodes, we intervene with supportive care. However, when recurrent episodes become a factor, we add Cosequin® (glucosamine-chondroitin) to the diet (see box, "The Efficacy of Chondroitin Sulfate in Treating Interstitial Cystitis"). Most owners simply open the capsule and sprinkle the contents onto the cat's food.

Cranny: When a cat is presented for the first episode, we discuss Cosequin supplementation with the client as a possible long-term adjunct to therapy. If there is a recurrent episode, I recommend that daily supplementation be initiated. The supplement is easy to administer with food and is well-tolerated by most cats.

Kruger: I have not used this product specifically but have used another glycosaminoglycan, Elmiron® (pentosan polysulfate). Pentosan has been used to treat interstitial cystitis in humans. Anecdotally, some cats with chronic idiopathic cystitis seem to have benefited from treatment with pentosan. However, we need to remember that the efficacy of most glycosaminoglycan products has not been evaluated in controlled clinical trials.

Table 1

Diagnostic Pitfalls to Avoid

- Do not catheterize patients with signs of nonobstructive lower urinary tract disease unless the benefits outweigh the risks associated with trauma to the mucosal surface and increased susceptibility to bacterial infection.
- Do not indiscriminately use antibiotics.
- Do not indiscriminately recommend acidifying diets because they may increase the risk for calcium oxalate urolithiasis.
- Do not formulate therapy for recurrent episodes of lower urinary tract disease based on the assumption that the underlying cause is always the same.
- Do not perform exploratory surgery and biopsy without a plausible plan of how the results will be of probable benefit to the patient.
- Do not treat chronic recurrent episodes of idiopathic cystitis by cauterizing or debriding the mucosal surface of the lower urinary tract.

Osborne: Dr. Levine, what is your opinion regarding the use of glycosaminoglycan supplementation?

Levine: When I initially heard the theory behind Cosequin therapy several years ago, I thought it made sense (see box, "The Theory Behind the Role of Cosequin Therapy"). Because the glycosaminoglycan layer is apparently disrupted in cats with idiopathic cystitis, administering the building blocks that restore this protective layer may be key to controlling this disease. When supplementation therapy is presented in this way to clients, most are eager to try it to restore and maintain bladder health. Clinically, I find it makes a marked difference. Most cats have fewer and less-severe episodes. The owners are pleased and return for more of the product. I do not believe that they would continue this treatment if they did not feel it was helping their cats. Using this product as a therapeutic measure is a good option to control an otherwise frustrating disease.

Welch: Cosequin therapy is well-accepted by cats because it is easy to give, thereby not subjecting cats to or introducing an additional stressor. The goal is to find a long-term, beneficial treatment, and this medical alternative seems to be a good candidate to explore further.

Osborne: Thus, although the clinical signs of idiopathic cystitis are often self-limiting, we need therapeutic alternatives for cats with frequently recurrent episodes and with persistent clinical signs. Based on the empirical observations of our colleagues, a randomized, controlled, double-blind clinical trial of Cosequin is clearly warranted. There is also a need for clinical trials to evaluate combinations of therapeutic agents, such as other glycosaminoglycans and amitriptyline. As we await the results of further investigations into the causes and treatment of idiopathic cystitis, we must also use caution to avoid diagnostic and therapeutic procedures that may be detrimental to our patients (*Table 1*). There are some patients we cannot help; there is no patient we should harm.