

# FIC (Feline Idiopathic Cystitis)

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### Incidence

The incidence of FLUTD in cats in the UK and USA is around 1%, with signs being seen most commonly in young to middle-aged cats. While there are a number of different conditions that can result in signs of FLUTD the vast majority of cases (55-69%) are idiopathic (Figure 1) (Kruger et al 1991; Buffington et al 1997; Lekcharoensuk et al 2001).

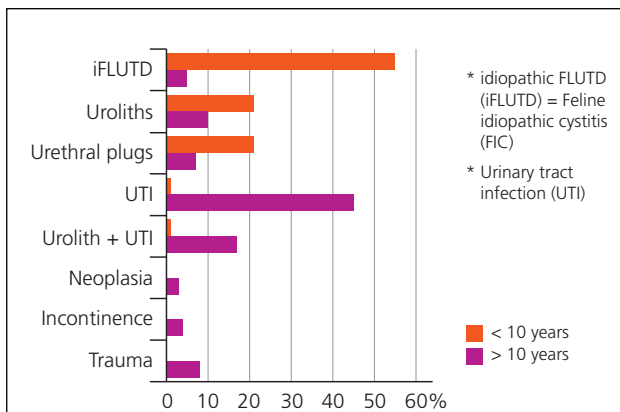


Figure 1.

Most common diagnoses in cats with signs of FLUTD, presented according to age (data from USA). (Bartges JW What's New in Feline LUTD? Proceedings of ECVIM 2002).

### Clinical signs

The clinical signs of Feline Lower Urinary Tract Disease (FLUTD) are:

- dysuria (straining)
- pollakiuria (increased frequency of urination)
- periuria (urination in inappropriate places)
- haematuria
- agitation or vocalisation when trying to urinate
- over-grooming the ventral abdomen and/or perineal area (presumably in response to local pain) and/or
- urethral obstruction.

Some cats present with behavioural change, loss of house-training, aggression and/or suspected constipation.

### Diagnosis

A diagnosis of feline idiopathic cystitis (FIC) is made when no other cause can be found (Hostutler et al 2005, Westropp 2006). Affected cats typically have concentrated, sterile urine, and unremarkable double-contrast bladder radiographs and urethral studies. However, it is important to remember that crystalluria is normal in any cat with concentrated urine; up to 1000 colony-forming units/ml of bacteria is considered as sterile even in urine collected by cystocentesis; and ~15% of cats with FIC have ventro-apical thickening of their bladder wall which can be seen on radiographs (Hostutler et al 2005).

### Pathophysiology

The pathophysiology of FIC is unclear, but disease is seen most commonly in young to middle-aged, over weight cats, that take little exercise, use an indoor litter box, have restricted access outside, eat a dry diet and, typically, live in a multi-animal household (where there is often antipathy between the affected cat and other members of the household) (Cameron et al 2004; Gunn-Moore and Shenoy 2004, Buffington et al 2006a). Clinical signs are often seasonal, being worse from autumn to early spring. Most non-obstructive cases have self-limiting episodes; usually resolving within 5-10 days, although occasional cases can be more prolonged.

*Current research suggests that FIC is seen when a 'susceptible cat is placed in a provocative environment'*

The changes in the bladder epithelium are believed to occur as an 'end stage' result of alterations in the cat's nervous and endocrine systems, leading to exaggerated arousal and an inability to cope with environmental stress.

The **primary cause** is unknown but is likely to be either genetic and/or developmental (the latter possibly related to early adverse experience). The end result is altered processing within the brain, changes in the nature of the adrenocortical response as a result



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of exposure to external events, and alterations in the interaction between the neuronal supply to and from the brain and the bladder. Subsequent changes in the integrity of bladder epithelium are exacerbated by compounds within the urine and altered interactions with the protective glycosaminoglycan (GAG) layer that lines the bladder (Figure 2) (Gluckman and Hanson 2004, Westropp and Buffington 2004, Westropp 2006, Fenton 2007).

**Stress** is believed to play an important role in triggering and/or exacerbating FIC, with suggested stressors including:

- Living in a multiple animal household (particularly when there is inter-cat conflict)
- Moving house
- Separation anxiety in indoor-only single-cat households
- Stress associated with urination (unsuitable litter box availability, access, position, type, content, hygiene)
- Abrupt changes in diet, weather or access outside
- The addition of new pets or family members (including new babies)
- Undertaking building work in the house
- Changes to the owners' work schedule
- Owner stress.

It is chronic rather than acute stress that appears to be most detrimental and reducing this may help to reduce the recurrence and/or severity of FIC.

Support for the importance of stress, and for exaggerated arousal, in the induction and/or maintenance of FIC comes from a number of **studies** that have shown that **affected cats respond to stress very differently from normal cats**.

**Normal cats**, when exposed to stressful situations, may show signs of fear, aggression, hiding, anorexia, and weight change. Physiologically, this stress results in activation of the hypothalamic-pituitary-adrenal axis. This is seen as increased activity in the hypothalamus, which produces corticotrophin-releasing factor (CRF) which acts on:

- i) the anterior pituitary to cause release of adrenocorticotrophic hormone (ACTH) which stimulates the adrenal glands to produce glucocorticoids from the adrenal cortex (i.e. cortisol) and
- ii) the brainstem nuclei and locus coeruleus (an area of the brain that deals with vigilance and autonomic activity), resulting in increased plasma catecholamine concentrations (causing enhanced adrenal sensitivity to ACTH) and activation of the sympathetic nervous system.

The role of glucocorticoids and other alpha-2 adrenoceptor agonists are very complex. However, one of their essential functions is to provide negative feedback to control the stress response, which they do by inhibiting further transmission of noxious signals to the brain, i.e. cortisol acts to dampen down the response by having an inhibitory action on the hypothalamus, anterior pituitary, brainstem nuclei and locus coeruleus.

In contrast, **cats with FIC**, when stressed, display more displacement activity than normal cats. This is seen as increased eating, drinking, grooming and urinating. Interestingly, while they do produce CRF and ACTH, they also develop a marked increase in activity in their locus coeruleus and sympathetic nervous system, but do not have increased plasma cortisol concentrations. The lack of cortisol results in a **lack of inhibition** within the brain and the peripheral sympathetic nervous system (Figure 2). This uncoupling of the hypothalamic-pituitary-adrenal axis is believed to result from desensitization or down-regulation of the alpha-2 adrenoceptor agonists receptors secondary to chronic stimulation (Buffington et al 1999, Westropp and Buffington 2004, Hostutler et al 2005, Westropp 2006, Westropp et al 2006, 2007).

Much of our understanding of the peripheral aspects of FIC has come from studying the **histopathology** of bladder wall biopsies taken from affected cats. They usually reveal a relatively normal epithelium and muscularis, but have submucosal oedema and vasodilation, without obvious inflammatory infiltrate, although large numbers of mast cells are frequently present. **Biopsies** often reveal increased numbers of unmyelinated pain fibers (C-fibers) and pain receptors (substance P receptors). These sensory neurones within the bladder wall are located in the submucosa; when stimulated these nerves transmit the perception of pain to the brain, and local axon reflexes lead to release of substance P, and other neurotransmitters), which can in turn result in:

- more pain,
- vasodilatation of the intramural blood vessels,
- increased vascular and bladder-wall permeability,
- oedema of the submucosa, smooth muscle contraction (resulting in a bladder and/or urethral spasm), and
- mast cell de-granulation.

Mast cell de-granulation results in the release of a variety of inflammatory mediators (including histamine, heparin, serotonin, cytokines, and prostaglandins) which can further exacerbate the effects of the C-fibres. Stimulation of C-fibres and the resulting neurogenic inflammation can therefore explain many of the changes recorded in FIC. The nerve endings can be stimulated in response to central triggers (such as "stress"), or via compounds within the urine (e.g. acid pH, potassium, magnesium, and

calcium ions). This in turn may result in further recruitment of C-fibres, and intensification of disease (Buffington et al 1999, Westropp and Buffington 2004, Hostutler et al 2005, Westropp 2006, Westropp et al 2006, 2007).

The thin layer of mucus (composed of GAG) which covers the bladder epithelium helps to prevent microbes and crystals from sticking to the bladder lining. Some cats with FIC have altered urine concentrations of GAG and increased urinary bladder permeability which may allow noxious substances within the urine to pass through the urothelium, so triggering the C-fibres and so causing inflammation (Buffington et al 1996).

- **In summary**, it is believed that FIC results from multiple complex abnormalities of the nervous and endocrine systems that affect more than just the bladder.
- The enhanced central noradrenergic drive and inadequate adrenocortical restraint maintains the chronic disease process and appears to be driven by increased hypothalamic CRF release due to a sensitised stress response system.
- This may result from a genetic accident and/or be an exaggerated response to early adverse experience.
- These cats are therefore poorly able to deal with chronic stress and resulting neurogenic inflammation of their bladder leads to the clinical signs of FIC.

**Management of FIC** may include

- Reducing stress**
- Dietary modification** and
- Drug therapy**

The cat's owner must appreciate that the aim of management is to reduce the severity and frequency of the episodes, but that cure is unlikely. Successful management needs a dedicated owner and a supportive veterinary team (Hostutler et al 2005). Unfortunately, few treatments have been investigated by well-controlled double-blinded experimental studies and since each episode of is usually self-limiting, many treatments may appear to be effective, when they are actually ineffective.

- There is no cure for FIC – only an attempt to minimise the signs.

- Reduce stress:**

Multimodal environmental modification (MEMO) is a promising adjunctive therapy for cats with FIC (Buffington et al 2006b). It

provides environmental enrichment which is tailored to the particular cat. Cats are naturally solitary hunters and have a relatively low requirement for social interaction. They naturally live in groups of related individuals and are hostile to the intrusion of cats from other social groups. Cats within the same social group will groom each other, rub on each other and/or curl up together, while cats in a different group will spurn physical contact, may hiss at each other or may simply ignore each other. Importantly, in terms of multi-cat households, social groups do not like to share essential resources and the provision of adequate and suitably distributed resources is a key factor in minimising social stress.

See the Indoor Cat Initiative website [www.indoorcat.org](http://www.indoorcat.org) or Westropp and Buffington 2004 for the questionnaire which will help the owner to understand exactly what cats need in general, what their cat needs in particular, and how this can best be achieved.

The five key resources are:

- Water stations,
- Feeding stations,
- Latrines sites or litter boxes,
- Resting places, and
- Points of entry and exit to and from the territory.

#### 1. **Social interaction, conflict, high resting places, escape routes and play**

Social stress is particularly relevant to cats living in multi-cat households; however, it should also be considered in single cat homes if there is evidence of tension with other cats in the neighbourhood. Issues such as visual access into or out of the home are often overlooked and these can be particularly effective at inducing chronic stress in cats living in highly populated areas (i.e. cats being able to see other cats through windows). Reducing stress for these individuals can be a challenge since not all factors are under the control of the owner. However, it can be beneficial to:

- pay attention to entry and exits points into the property,
- invest in microchip controlled cat flaps,
- restrict visual access into and out of the home by covering windows with semi-opaque coverings, and
- modify the availability of resting places on window ledges and in the garden (so that inside cats cannot see out and/or outside cats cannot see in).

When cats find themselves in situations of tension their natural **coping strategy** is to escape to a safe location. The provision of safe escape routes within multi-cat households is essential, as is adequate provision of resting places and elevated positions (such as climbing posts and the top of cupboards). The opportunity to hide and have periods of privacy is also important.

Disputes over **entry and exit points** can be a source of chronic stress and it is not uncommon for cats to be denied access into the home by incompatible individuals within the household. Provision of separate entry and exit points can therefore be an important part of the environmental management. If one cat is particularly aggressive then putting a bell on its collar may alert the FIC-sufferer to its presence and allow it time to escape.

One way in which feline perception of the home can be enhanced is through the use of **pheromones** (Gunn-Moore and Cameron 2004). One of the fractions of the feline facial pheromone complex (F3) is available in a synthetic form (Feliway™, Ceva Animal Health). This so called “familiarisation pheromone” serves to decrease perception of threat and increase a sensation of safety within the home. It is applied to the environment via a diffuser device which is designed to be switched on for 24 hours a day in order to obtain an even distribution of the pheromone throughout the house.

### *Environmental enrichment often means increasing the amount of play a cat undertakes*

Different cats require different degrees of **interaction with their owners**. Some cats are almost completely self-dependant, while others enjoy being petted and/or groomed, and like to play games. This should be introduced as short sessions each day and include games that stimulate natural cat behaviour, such as the provision of paper bags and boxes to play in, fishing rod toys to chase, and hunting games (e.g. hiding toys filled with cat nip or little bits of food). It is important that the owner (and other members of the cat’s household) interacts consistently with the cat and that they do not punish it.

- Environmental enrichment should include opportunities for scratching, climbing, hiding, resting, and play
- Encourage owners to provide separate resting places for cats in multiple locations throughout the house, some in elevated positions

## 2. Food

Feeding is not a social behaviour in cats and most cats prefer to eat their meals in private. The common approach of feeding cats at set meal times is not only inappropriate from a physiological perspective; it also brings all of the cats into a small area at the same time, which significantly increases social tension. Provision of ad lib or self service style feeding favours more natural feeding behaviour and offers cats the chance to feed alone. This can be further enhanced by providing multiple feeding stations around the house.

- Encourage owners to provide separate eating areas in different locations throughout the house.
- If the type of food needs to be changed, this should be done by providing a separate bowl next to the original food bowl, so the cat has a choice and can indicate their preference.
- Change should be made very gradually. If the cat becomes stressed by the diet change then it may, in some cases, be better to leave the cat on the preferred diet (see the Indoor Cat Initiative for tips of changing diets in cats with FIC: [www.indoorcat.org](http://www.indoorcat.org)).

## 3. Water

Reducing urine specific gravity can significantly reduce the risk of recurrence of FIC and reduce the severity of the episodes (Markwell et al 1999; Gunn-Moore and Shenoy 2004). This can be achieved by feeding a wet diet and/or encouraging cats to drink more water.

*Different social groups are unlikely to share water stations so it is important to provide an adequate number and location for each of the social groups living in the household.*

Cats generally prefer to eat and drink in separate locations so containers which encourage the provision of food and water directly adjacent to one another should be avoided. In order to decrease the risk of water taint and increase the visibility of the surface of the water it is best to avoid containers made of plastic and those that offer only a small surface area. Instead, cats should be provided with large water bowls (with a large surface area)

made from glass, ceramic or metal. Most cats like to avoid shadowing the surface of the water as they drink so they do not like putting their head directly over the top of the receptacle, or inside it. This means that cats rarely drink from water bowls that are not entirely full and it is important to keep the water filled up to the top at all times. Moving water is generally more attractive than still water so the provision of a 'pet water fountain' or access to a dripping tap should be considered. If owners are still finding it difficult to encourage drinking they can consider offering fish or chicken stock and diluting cat food to form 'soup'. (N.B. Do not use stock cubes designed for human consumption as they usually contain large amounts of onion powder which can result in Heinz-body anaemia in cats).

- Supply free access to water and encourage the cat to drink.
- Cats typically select water on freshness, taste, movement (water fountains, dripping faucets etc) and the shape of the container (most cats prefer a wide container, but others like drinking from a regular glass or cup).

#### 4. Litter boxes

Stress associated with urination can be particularly significant for cats suffering from FIC. It is therefore important to provide a safe and secure area in which the cats can toilet and to ensure that litter boxes are positioned in locations that offer privacy.

*An appropriate number of boxes is important as cats should not be expected to share with cats from other social groups. Even more important than the number of boxes is the number of litter-box locations and these should be matched to the number of social groups within the household*

The positioning of the boxes should allow the cats to have free and immediate access without having to meet other cats. It is not good having two boxes positioned side by side if the two cats in the house do not form a single social group. While covered litter boxes may provide a safe and private place to eliminate, many cats do not like them as cats from different social groups may try to pounce on them as they leave the box.

Cleaning regimes should be adequate to ensure that all boxes are sufficiently clean to encourage regular use. Daily scooping of urine and faeces is essential and full cleaning of the box and replacement of the litter should take place at least once a week. The litter type should be selected to maximise substrate preference and those litters which are perfumed or uncomfortable underfoot should be avoided. Since the depth of the litter has been shown to be important in encouraging the use of the box owners should be encouraged to invest in deep sided boxes and to use sufficient quantities of litter to ensure adequate digging and burying behaviour during elimination.

- Litter boxes should be provided in different locations throughout the house and placed in quiet convenient locations.
- If testing different types of litter, offer them side by side in separate boxes, so the cat can indicate their preference.

#### ii) Dietary modification

Altering the diet most easily modifies the content of cat urine. While much interest has been placed on altering the urine pH, and its magnesium and calcium content, it is now believed that the most important factor in reducing signs of bladder discomfort is the rate of water turnover (Markwell et al 1999; Gunn-Moore and Shenoy 2004). However, while reducing the urine specific gravity will reduce the signs of bladder pain it is unlikely to alter the underlying pathology of FIC; stress reduction is still needed to address this. The aim of dietary manipulation is therefore to create less concentrated urine (specific gravity ~1.035) which encourages more frequent urination and dilutes any noxious components within the urine.

Rather than altering the content of a dry diet, it is generally advisable to feed a wet one. However, not all cats will eat wet diets. A number of diets have therefore been designed in both wet and dry forms that can result in increased water consumption, and reduced urine specific gravity and relative supersaturation (RSS). Some achieve this by adding high levels of salt (NaCl) (e.g. Royal Canin Urinary SO and Purina UR ST/Ox) while others choose a different route (Hill's c/d Multicare) - a combination of adding potassium citrate, extra vitamin B6 (to reduce oxalate formation), adding omega-3 and 6 fatty acids (to reduce inflammation, among other things), and adding vitamin E and beta-carotene (as antioxidants). These diets can effectively decrease urine specific gravity and RSS and so reduce bladder inflammation in cats with FIC.



While diets high in salt are often effective in the short term, we do not, as yet, know their long-term consequences; although it is known that high salt diets should not be given to cats with kidney disease.

- Feeding wet food can significantly reduce the specific gravity and RSS of the urine, and so reduce the episodes of FIC.
- Ideally, dry food should gradually be changed to an appropriate wet food (see the Indoor Cat Initiative for tips of changing diets in cats with FIC: [www.indoorcat.org](http://www.indoorcat.org)).

### iii) Drug therapies:

A number of drugs may be used in the management of FIC;

- anti-spasmodics,
- analgesics,
- GAG supplements, and
- tricyclic antidepressants.

1. **Anti-spasmodics** may be used to relax urethral spasms that occur in some male cats with FIC. Spasms may be initiated by local pain or inflammation, and may affect the smooth and/or skeletal muscle of the bladder and urethra. While these drugs are rarely associated with side effects in young cats, the risk of concurrent renal or cardiac disease should be assessed before they are given to older cats. Injectable drugs (e.g. ACP) may be given at the time of relieving a urethral obstruction, after which the author commonly prescribes a 7-14 day course of prazosin (and, in very severe cases, dantrolene). These two drugs can be given together, and longer or intermittent courses of prazosin may be required in some cases. The author prefers to wean off these drugs over a few days rather than stopping them suddenly, usually stopping the dantrolene before the prazosin.

- Smooth muscle anti-spasmodics include:
 

Acepromazine	0.05-0.2 mg/kg IV, IM, SC or 1-3 mg/kg PO
Prazosin	0.25-1.0 mg/cat PO q8-12h
- Skeletal muscle anti-spasmodics include:
 

Dantrolene	0.5-2.0 mg/kg PO q12h
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### 2. Analgesia and anti-inflammatory drugs:

While these drugs may reduce the severity of the clinical signs they should always be combined with environmental and dietary modifications.

- NSAIDs appear to help in many cases:
  - Meloxicam 0.1 mg/kg PO q24h for 4 days, then 0.05 mg/kg PO q24h longer term as needed
- Buprenorphine can help short-term:
  - 10-30 ug/kg PO, SQ, IM or IV q8-12h.

### 3. GAG supplements:

While the one published double-blinded controlled study showed these had little positive effect, some individual cats appear to have positive responses (Gunn-Moore and Shenoy 2004). This probably indicates that only a subgroup of cats with FIC will benefit from GAG supplementation; different types of GAGs may produce different effects.

In the one published study the author gave N-Acetyl Glucosamine, which is a precursor for GAG (125mg per cat PO q24h). However, it can also be given at higher dose at the time of the initial presentation, and then reduced to a maintenance level.

4. **Tricyclic antidepressants (TCA)** may give positive effects in some cats with FIC.

However, the two well-controlled studies have shown that short courses (seven days) may actually increase the risk of recurrence (Kraijer et al 2003, Kruger et al 2003). Unfortunately, there are no published well-controlled studies on their longer term use; in other aspects of behavioural medicine the clinical effects of these drugs do not generally become apparent until after the fourth week of treatment so it is still possible that long term treatment may be beneficial. TCAs have both behavioural and organic effects;

- Anticholinergic (including increasing bladder capacity),
- Anti-inflammatory (including preventing histamine release from mast cells),
- Anti-alpha adrenergic,
- Analgesic and
- Antidepressant effects.

They should be used with caution in cats, and reserved for those cases with very severe or chronic disease, or when a potential source of stress can be predicted but cannot be avoided e.g. moving home or a stay in the cattery.

Amitriptyline 0.5-1.0 mg/kg PO q24 hours (evening); wean down to as low a dose as possible.

Clomipramine 0.25-0.5 mg/kg PO q24 hours (evening); wean down to as low a dose as possible.

Side effects include somnolence, urinary retention, and raised liver enzymes. Liver function should be assessed prior to starting therapy, reassessed one month later, and then every 6-12 months while the cat is on treatment.

### Summary of FIC management:

It is important to remember that all current treatments for FIC are merely palliative. The best results are gained by instigating a number of changes, i.e. reducing stress and paying particular attention to the issue of social stress, feeding a wet diet, increasing water intake by providing behaviourally sound water stations, and if necessary, relieving urethral spasm and possibly replacing GAGs. In most cases, when tailored to the individual cat, this will reduce or prevent further clinical signs. TCA's should only be used in very severe recurrent cases. Referral to a veterinary behaviourist may be necessary in order to accurately identify and resolve sources of chronic stress.

Where possible, it helps to be proactive. This can be achieved where observant owners are able to notice their cat showing prodromal signs before an episode of FIC becomes clinically obvious. The duration of these signs may vary from a few days to a few hours, and may include increased perineal and hind-end grooming, or altered behaviour (often seen as inter-cat aggression

initiated by the FIC-sufferer). These signs probably relate to increasing perineal and/or bladder pain. Making or reinforcing management changes at this time may help to reduce the severity and duration of the episode, i.e. further reduce stress (give the cat more attention and cuddles, install a Feliway™ diffuser [or replace the empty one], increase fluid intake, and/or giving Meloxicam, prazocin or a GAG supplement, or increase their dosage. This approach can also be used if a stressful episode is anticipated, (e.g. a visit to the vet, a stay in a cattery, builders in the home, etc.), where in addition to the changes mentioned Feliway™ spray can be applied to cat carriers or cattery cages.

### Prognosis

The prognosis for cats with FIC depends on the severity of the clinical signs and the gender of the cat. FIC without obstruction rarely proves fatal, that is, unless the owner feels the cat's quality of life is so poor that they opt for euthanasia. However, 30-60% of affected cat may show repeated episodes of FIC (Markwell et al 1999, Gunn-Moore and Shenoy 2004). Male cats that develop urinary obstruction carry a significant risk of recurrent disease, with ~50% continuing to show clinical signs of bladder discomfort, ~30-40% re-obstructing, and ~20% will being euthanased because of continued disease (Gerber et al 2008).

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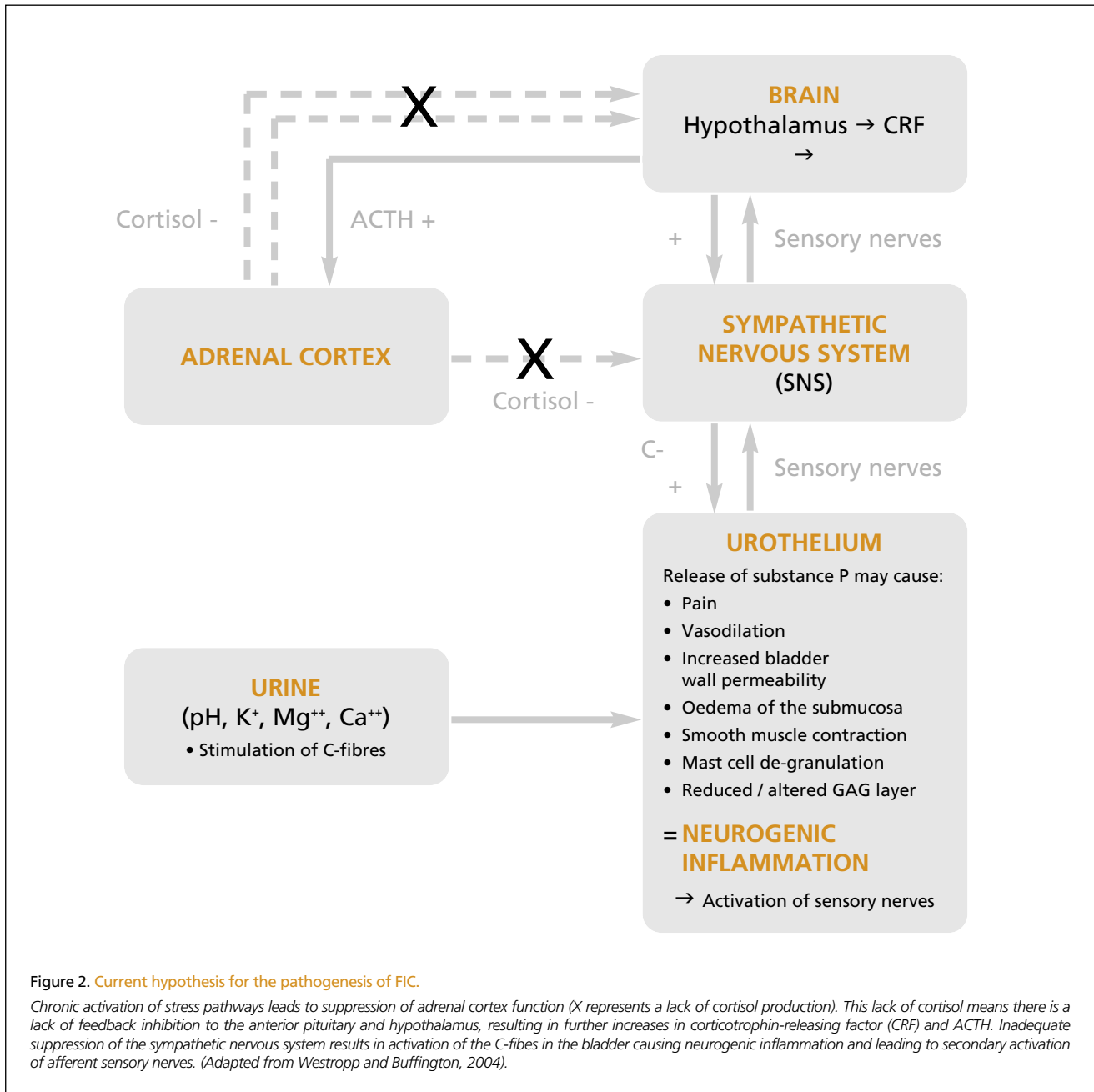
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**Figure 2. Current hypothesis for the pathogenesis of FIC.**

Chronic activation of stress pathways leads to suppression of adrenal cortex function (X represents a lack of cortisol production). This lack of cortisol means there is a lack of feedback inhibition to the anterior pituitary and hypothalamus, resulting in further increases in corticotrophin-releasing factor (CRF) and ACTH. Inadequate suppression of the sympathetic nervous system results in activation of the C-fibres in the bladder causing neurogenic inflammation and leading to secondary activation of afferent sensory nerves. (Adapted from Westropp and Buffington, 2004).