

Interstitial Cystitis and Lower Urinary Tract Symptoms in Males and Females—The Combined Role of Potassium and Epithelial Dysfunction

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Evidence of a lower urinary tract dysfunctional epithelium has been detected in women and men with interstitial cystitis and other complexes of lower urinary tract symptoms. Lower urinary tract dysfunctional epithelium can affect the bladder, the urethra, the labia or vaginal introitus in women, and the prostatic ducts and urethra in men. Because an individual with lower urinary tract dysfunctional epithelium may experience pain in one or more locations throughout the pelvis in any combination, the clinician cannot reliably establish a diagnosis based on “where it hurts.” A useful diagnostic tool is the intravesical potassium sensitivity test, which detects the abnormal epithelial permeability of lower urinary tract dysfunctional epithelium. In most cases, lower urinary tract dysfunctional epithelium can be treated successfully. [Rev Urol. 2002;4(suppl 1):S49–S55]

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In evaluating a patient with lower urinary tract symptoms (LUTS), urologists have tended to name the problem according to where the patient hurts. For example, an individual with urethral pain is considered to have urethritis; an individual with urgency/frequency and pain in the bladder is diagnosed as having some type of cystitis. A man with penile tip pain and perineal pain that may be associated with sexual intercourse is considered to have prostatitis. In fact, all of these symptomatic genitourinary syndromes are likely linked by an epithelial dysfunction. This dysfunction results in abnormal permeability of the urothelium, which allows the normally high levels of urinary potassium to diffuse into the interstitium and directly depolarize sensory nerves, creating urgency and/or pain.

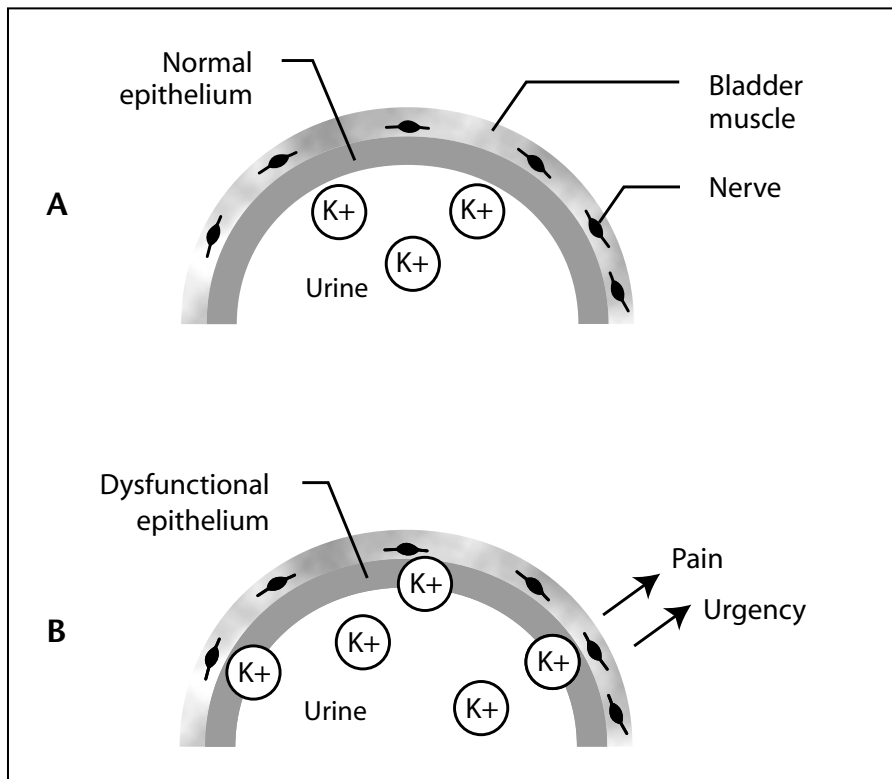


Figure 1. A healthy bladder epithelium (A) prevents urinary potassium from penetrating to the underlying muscle, but an abnormally permeable epithelium (B) allows potassium to leak into the interstitium, depolarizing nerves and muscle and causing urgency and/or pain.

This epithelial dysfunction can be detected using the intravesical Potassium Sensitivity Test (PST). In several published studies, we have administered the PST to several symptomatic populations, including patients diagnosed with acute bacterial cystitis, detrusor instability, radiation cystitis, interstitial cystitis (IC), chronic pelvic pain (in females), and suspected bladder outlet obstruction (BOO) due to benign prostatic hyperplasia (BPH) in men. In this review, we summarize those results and present a view of the patients' disease as lower urinary tract dysfunctional epithelium (LUDE) disease, manifested by a variable symptomatic presentation but a consistent finding: intravesical potassium sensitivity and probable urethral sensitivity.

LUDE disease encompasses not

only the majority of cases of IC but also substantial numbers of cases diagnosed as LUTS or chronic pelvic pain in both women and men. It is extremely important to detect LUDE, not only because it appears to affect large numbers of individuals but also because the disorder can often be

treated with success, particularly in its early stages.

Epithelial Dysfunction

In a healthy bladder, a mucus lining containing glycosaminoglycans (GAGs) and glycoproteins forms a barrier that prevents urine and its contents from leaking through the

urothelium and damaging the underlying sensory nerves and muscle.¹ In most IC patients, however, we have found that the urothelium has an abnormal degree of permeability that allows potentially harmful substances in urine to penetrate to the bladder muscularis.²⁻⁶

One potentially damaging urinary solute is potassium, which is present in high levels (40–140 mEq/L) in normal urine. A healthy urothelium prevents potassium from migrating across the urothelium so that the bladder nerves and muscularis are protected from injury (Figure 1A). If a dysfunctional epithelium allows the diffusion of potassium into the bladder interstitium, however, the potassium can depolarize nerves and muscle and lead to tissue injury (Figure 1B).⁶ This process produces the symptoms of urinary urgency and/or pain.

Potassium Sensitivity Test

On the basis of the epithelial permeability model, we developed the PST, in which the bladder is challenged with two separate intravesical solutions, one of sterile water and one of potassium.^{6,7} In response to the potassium challenge, a healthy individual who has an effective urothelial permeability barrier suffers no urinary symptoms (urgency and/or pain),

The disorder can often be treated with success, particularly in its early stages.

because the potassium does not penetrate the urothelium (Figure 1A). An individual with an abnormally permeable epithelium, however, experiences urgency and/or pain symptoms in response to the instillation of potassium as the potassium passes through the urothelium and penetrates into the bladder interstitium (Figure 1B).

Table 1
Pain Locations in Women and Men with LUDE Disease

Pain Location*	Frequency in Females with Urethral Syndrome [§]	Frequency in Females with IC (n = 424) [§]	Frequency in Males (n = 108) [†]
I. In women and men			
Dysuria	43/81 (47%)	246/424 (58%)	56/108 (52%)
Above pubic bone	54/81 (67%)	250/424 (53%)	46/108 (42%)
Lower abdomen	36/81 (45%)	199/424 (47%)	43/108 (40%)
Lower back	34/81 (42%)	148/424 (35%)	20/108 (18%)
Inguinal	19/81 (23%)	119/424 (28%)	49/108 (44%)
Pain with sex [‡]	54/91 (59%)	219/312 (71%)	44/62 (71%)
II. In women only			
Vaginal	42/81 (52%)	216/424 (51%)	
Urethral/vaginal	56/81 (71%)	322/424 (76%)	
III. In men only			
Scrotum/testes			43/108 (40%)
Penis/urethra			51/108 (47%)
Perineal			55/108 (51%)
No pain			24/108 (22%)

* The three sections show pain areas present in both women and men (Part I) and genital pain areas specific to women (Part II) and to men (Part III).

[†] Over a 12-year period.

[‡] In those sexually active.

[§] Data from Parsons et al.²

Only 0% to 4% of healthy individuals experience symptoms of urgency or pain in response to intravesical potassium; when such symptoms do occur in normal controls, they are mild. If a normal subject undergoes a PST after experimental injury to the epithelium, however, he or she absorbs potassium and experiences symptoms of urinary urgency and/or pain, a reaction that can be reversed by a brief treatment with heparin.⁶ It is important to understand that urgency and pain are an abnormal response to intravesical potassium. The potassium solution can cause

urgency or pain only by diffusing across the normally impermeable bladder epithelium. Therefore the only way a person can be potassium sensitive is with a dysfunctional epithelium. For this reason, a positive PST can be considered a valid indicator of abnormal epithelial permeability.

Variable Presentation of Pelvic Pain in Men And Women

In our studies of IC in both women and men, we have found that the pain of IC is not restricted to pain with voiding (dysuria). Although differences in male and female perineal

anatomy make it impossible to compare IC pain location by location in the two genders, it is clear that IC pain can refer to locations throughout the pelvis, including the urethra, the vagina (in women), the penis, testes, and/or scrotum (in men), the suprapubic area, the lower abdomen, the lower back, and the inguinal area, in any combination² (Table 1). In addition, of the men in our study who reported IC pain, 80% reported pain in two or more locations. The rate of dysuria in men (52%) suggests that epithelial permeability probably cycles in the urethra as well as in the bladder in IC.

Table 2 presents the results of potassium sensitivity testing in populations of women and men with IC. The women and men exhibited similar rates of positive PST as well as similar median values for the pain and urgency they experienced in response to the potassium instillation during the PST.

In our experience in treating over 5000 individuals with IC, we have found that the presenting symptoms depend on the gender of the patient, the tissues affected (and therefore the body area in which the patient experiences any IC pain), the stage of the disease, and variations in factors that can provoke IC symptom flares, such as seasonal allergies or (in women) the menstrual cycle.

Results of Potassium Sensitivity Testing in Symptomatic Patients

To date, a variety of centers have published the results of over 1500 PSTs. Overall, approximately 80% of IC patients tested have been PST-positive. In one study, diagnosed IC patients had a 78% rate of positive PST.² The rate of positive PST in patients diagnosed with "urethral syndrome," which we consider early IC, was a lower but still significant 55%. None of the controls had a positive

Table 2
Results of Potassium Sensitivity Testing in Females and Males

Parameter	Females with Urethral Syndrome (n = 116) [†]	Females with IC (n = 466) [*]	Males (n = 52)
Positive PST	64/116 (55%)	362/466 (78%)	43/52 (82%)
Median urge response*	2.58	3.54	2.7
Median pain response*	1.95	3.58	3.0

* On PST analog pain and urgency scales where 0 = no pain/urgency and 5 = severe pain/urgency.

[†] Data from Parsons et al.²

PST. We believe that most individuals with IC have a bladder epithelial dysfunction whose severity depends not only on the phase of the disease but also on variable factors that can provoke symptom flares and likely intermittent epithelial dysfunction.

In addition to our PST studies in IC patients, we have administered the PST to individuals diagnosed with a variety of other genitourinary disorders,

all involving the symptoms of urinary urgency and/or pain. The results of potassium sensitivity testing in these various groups of symptomatic patients are reviewed here and summarized in Table 3 and Figure 2.

In a 1994 publication,⁷ we reported the results of PST testing in IC and radiation cystitis patients. In that study, we detected positive potassium sensitivity in 70% of IC patients and

100% of radiation cystitis patients, indicating the presence of an epithelial permeability defect in those individuals. In the radiation cystitis patients, the PST detected the epithelial permeability defect occurring secondary to radiation-induced microvascular damage. These results support the hypothesis that IC is not the only lower urinary tract syndrome that involves altered epithelial permeability.

We obtained further evidence of this in a study of potassium sensitivity in IC patients and in individuals with a variety of other sensory disorders of the bladder.⁶ As detailed in Table 3, the data indicated positive potassium sensitivity in 74% to 76% of patients with IC as well as 25% of patients with detrusor instability, 100% of patients with acute bacterial urinary tract infection (UTI), and 3% of patients with BPH. In the same study, we measured potassium sensitivity in normal subjects before and after experimental injury of the bladder epithelium (see below).

In 2001 we reported results of

Table 3
Rates of Abnormal Epithelial Permeability Detected in Populations of Symptomatic Urologic and Gynecologic Patients

Population	Number in Group			Number PST Positive (%)
	Females	Males	Total	
Urologic—acute bacterial cystitis*	—	—	4	4 (100%)
Urologic—detrusor instability*	—	—	16	4 (25%)
Urologic—radiation cystitis [†]	—	—	4	4 (100%)
Urologic—"urethral syndrome" [‡]	116	0	116	64 (55%)
Urologic—IC [*]	466	0	466	362 (78%)
Gynecologic—chronic pelvic pain [§]	134	0	134	114 (85%)
Urologic—lower urinary tract symptoms (LUTS)	25	526	551	89 (16%)

* Data from Parsons et al.⁶

[†] Data from Parsons et al.⁷

[‡] Data from Parsons et al.²

[§] Data from Parsons et al.³

^{||} Data from Bernie et al.⁴

potassium sensitivity testing in 134 women who consulted gynecologists for chronic pelvic pain.³ We found that 85% of these patients were PST-positive, a rate consistent with PST results in urologic IC patients. These women had received gynecologic diagnoses ranging from endometriosis to yeast vaginitis upon initial evaluation. Only 2.9% of the patients had received an initial clinical diagnosis of IC, but 75% of them reported when surveyed that they had genitourinary symptoms of urgency-frequency. Our findings in this study suggest that LUDE disease is present and unrecognized in a significant number of gynecologic pelvic pain patients. As over 9 million women in the United States suffer from chronic pelvic pain,⁸ the number of affected individuals may be substantially greater than is currently realized.

In another study reported in 2001, we administered PSTs to a largely male population of patients undergoing urodynamic evaluation for lower urinary tract symptoms (LUTS) at a large Veterans Administration medical center.⁴ The most common diagnosis in older men with LUTS is BOO secondary to BPH; we performed the study to determine whether IC might account for symptoms in some of these patients. Of the 551 LUTS patients tested, 16% were PST-positive. Relative to the PST-negative LUTS patients, the PST-positive patients showed urgency at significantly lower volumes, a lower bladder capacity, and a lower postvoid residual upon urodynamic testing. The results suggest that a different pathology may be present in the PST-positive LUTS patients from that in the PST-negative patients, and that the LUTS population may be another area in which undetected cases of LUDE disease may exist. This would increase the LUDE disease patient population pool by adding 1 out of 6 BOO patients to the mix.

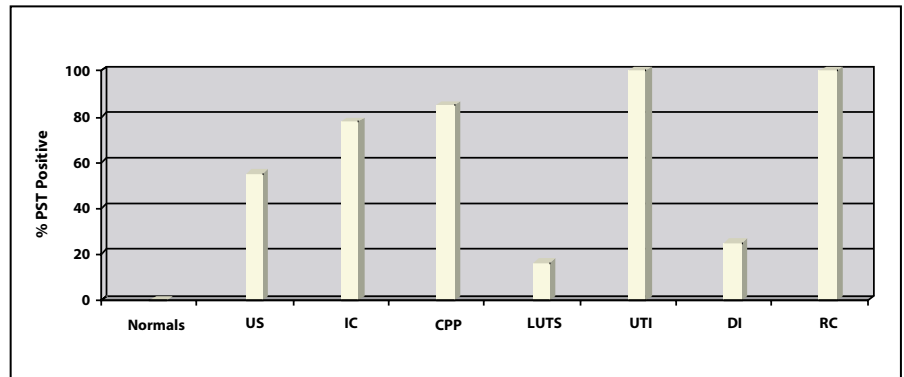


Figure 2. Rates of positive potassium sensitivity in normal controls and in populations of symptomatic patients. US, urethral syndrome; IC, interstitial cystitis; CPP, chronic pelvic pain; LUTS, lower urinary tract symptoms; UTI, acute bacterial urinary tract infection; DI, detrusor instability; RC, radiation cystitis.

We also determined rates of positive PST in 466 patients with clinical IC and 116 patients with “urethral syndrome.”² The IC patients met the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIDDK) criteria for diagnosis of IC,⁹ with the exception of the urodynamics evaluation; the urethral syndrome patients had had intermittent urgency/frequency and bladder or pelvic pain for less than 6 months. The rate of positive PST was 78% in the IC patients and 55% in the urethral syndrome patients. In this same study, we surveyed the patients for dyspareunia and documented the location(s) in which they perceived their genitourinary pain. The results are summarized in Table 1. From these results, we concluded that an epithelial permeability defect underlies both IC and “urethral syndrome” and that “urethral syndrome” is actually early IC. Of 42 control subjects in the study, none had a positive PST.

These PST results from various symptomatic populations indicate that a single pathophysiologic process, a dysfunctional lower urinary tract epithelium, underlies a variety of problems for which patients consult urologists or gynecologists. For any given patient, we can look at the clinical situation to determine the

specific etiology. For example, a patient receiving radiation therapy for bladder cancer may develop radiation cystitis, which gives rise to a secondary bladder epithelial dysfunction that, together with the potassium, produces the patient’s symptoms of urgency and pain.

A positive PST should be considered a definitive sign of LUDE disease. A negative PST, however, should not be regarded as confirmation that LUDE disease is absent. Because of the variable nature of the symptoms of LUDE disease, a patient with this disease may test PST-negative on any given day. Treatment should not be withheld from a PST-negative patient who has symptoms of LUDE disease in the absence of other definable pathology. The finding of a positive PST is quite useful to the clinician, especially in a patient for whom one is not sure of a diagnosis (for example, BPH, prostatitis, testalgia).

Results of Potassium Sensitivity Testing in Normal Controls

Normal control subjects show an extremely low rate of positive potassium sensitivity. In a 1998 study,⁶ we administered the PST to a group of normal subjects and to a second group of normal subjects who underwent experimental injury of the

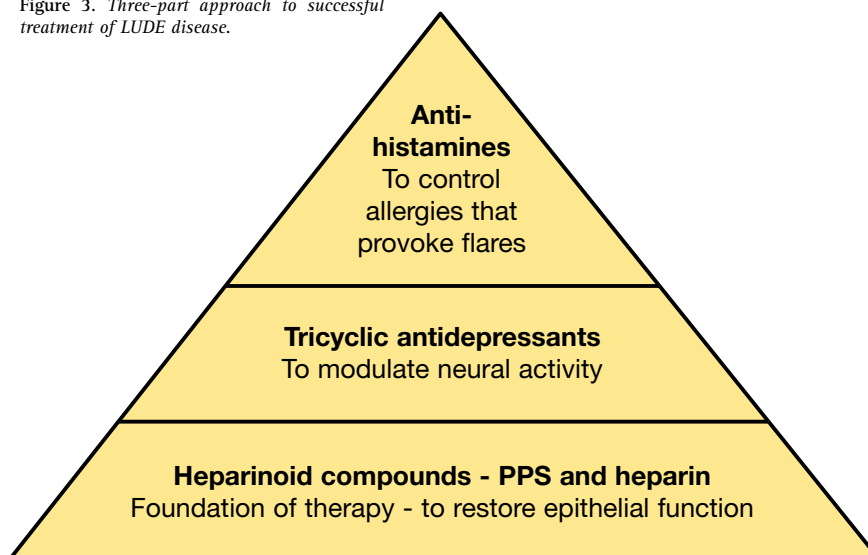
bladder epithelium with protamine sulfate. A positive PST was detected in only 4% of individuals with an intact urothelium. Of 19 normal individuals after urothelial injury with protamine, however, 15 (79%) experienced urgency in response to intravesical potassium, and 7 (37%) experienced pain. After heparin was instilled intravesically, the rate of urgency declined to 42% and pain to 11% in these individuals. These results confirmed that pain and urgency are an abnormal response to potassium instillation and occur only if an urothelial injury is present. In the same study, we found that intravesical instillation of sodium chloride provoked urgency in only 1 of 10 normal control subjects whose bladders were experimentally injured, while potassium provoked urgency in 9 of the 10 controls.

Treatment of LUDE Disease

In the author's experience in treating over 5000 patients with IC, good control of the disease can be achieved in up to 85% to 90% of IC (LUDE) patients. Depending on the clinical status of the individual patient, a successful treatment regimen consists of up to three components (Figure 3).

The heparinoid compounds oral pentosan polysulfate (PPS)¹⁰⁻¹⁵ and intravesical heparin¹⁶ are the foundation of treatment of LUDE. PPS and heparin are similar in structure to the

Figure 3. Three-part approach to successful treatment of LUDE disease.



glycosaminoglycans that regulate epithelial permeability at the surface of the normal bladder. It is believed that such compounds may compensate for the dysfunction present in the natural mucus of the lower urinary tract.¹⁷ Hence these drugs correct a primary component of the disease, the epithelial abnormality.

PPS, which has undergone extensive clinical evaluation, appears to be the most successful mode of treatment available for IC (LUDE). Results of the most recent studies^{14,15} indicate that the duration of PPS treatment is generally more important than the dose. In one study,¹⁵ an 8-month course of PPS therapy resulted in a 67% rate of improvement, and the

fact that the rate of response was still rising at the end of the study suggested that continued therapy would have yielded an even higher response rate. In our experience, the response rate at the end of 1 year of PPS therapy is 75% in patients with mild to moderate disease. To make it easier for the patient to remember, we routinely prescribe a dose of PPS 200 mg twice a day in females, but 100 mg 3 times a day works well. A higher dose may be required in some individuals, however; for example, in males, for whom we routinely prescribe 300 mg twice a day. In patients with mild to moderate disease, response to PPS therapy should be judged only after at least a year. In patients with

Main Points

- Women and men with a variety of urgency and/or pelvic pain symptoms show evidence of a lower urinary tract dysfunctional epithelium (LUDE).
- LUDE can affect tissues in the bladder, the urethra, the labia or vaginal introitus in women, and the prostatic ducts and urethra in men.
- Because the pain of LUDE can occur in locations throughout the pelvis in any combination, patients with the disease cannot be diagnosed according to where it hurts.
- The potassium sensitivity test detects lower urinary tract epithelial dysfunction and can be a useful tool in establishing a diagnosis.
- LUDE disease can be treated successfully in many affected patients.

severe disease, such assessment should be done only after at least 2 years of therapy. The only drugs shown to have long-term efficacy for treatment of IC (LUDE) are PPS and heparin. On a physiologic basis, in theory, PPS should reverse the course of the disease toward normal.

PPS should be used in combination with drugs that address the allergic and neurologic components present in many patients with IC. To control any allergies that promote IC symptom flares, the antihistamine hydroxyzine should be used at a dose of 25 mg at 6:00 in the evening to minimize the impact of its sedative effects. To reverse the neural activation in the bladder, which may be particularly severe in individuals with long-standing disease, the patient should be given an antidepressant such as amitriptyline.

Summary

A male or female patient at the age of 50 years or under who presents to a urologist's office with urgency/frequency and/or pelvic pain is at high risk for having LUDE disease and likely has a problem with potassium metabolism in the lower urinary tract. In such patients, the disease

may affect any particular organs or tissues in the lower urinary tract—the bladder, urethra, or prostate—and in any combination, and is reflected in the patient's symptoms. A man with penile pain, for example, may have the urethral component of the disorder. By understanding the disease process and using the PST, which is a relatively specific provocateur of the urinary symptoms of urgency and/or pain in those individuals with suspected LUDE disease, we can diagnose and offer these patients extremely successful therapy, primarily heparinoid therapy. ■

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