



Cystistat[®]

Sodium hyaluronate 40mg/50mL

Interstitial Cystitis



Interstitial Cystitis/ Painful Bladder Syndrome (IC/PBS), is a devastating disease that, without adequate therapy, leads to a state of unremitting pain and urinary frequency up to 70 times a day. The multifactorial etiology and obscure pathogenesis as well as too rigid and restrictive diagnostic criteria in the past are responsible for the fact that controlled studies on IC/PBS therapies are rare and include only small numbers of patients that are heterogeneous as to their symptoms and duration of disease. Thus, present therapeutic recommendations are mainly based on empiric data.

-- Riedl et al

What is Interstitial Cystitis



Interstitial cystitis (IC) is a chronic, non-bacterial, inflammatory disease of the bladder with very painful, distressing and sometimes debilitating symptoms.

The symptoms may initially resemble a bacterial infection of the bladder, but the urine is sterile.

Terminology

2003 IC/CPPS (chronic pelvic pain syndrome)

2004 IC/PBS (painful bladder syndrome)

IC: characteristic symptoms (1)

- **Pain:** lower abdominal (pelvic) pain
- **Urgency** constant intense urge to urinate
- **Frequency** Frequent urination, including night



IC: Symptoms (2)



- **Pain that increases as the bladder fills**
- **Emptying the bladder usually alleviates the pain and gives a temporary sense of relief**
- **Suprapubic pain**
- **Lower abdominal (pelvic) pain**
- **Sometimes pain in the lower part of the back**
- **Pain may also be felt in the groin and the thighs**
- **In women: there may be pain in the vagina**
- **In men: pain in the penis, testicles, scrotum and perineum**
- **Both men and women may have urethral pain**
- **There may be a constant, often intense urge to urinate**
- **Frequent urination, including at night.**

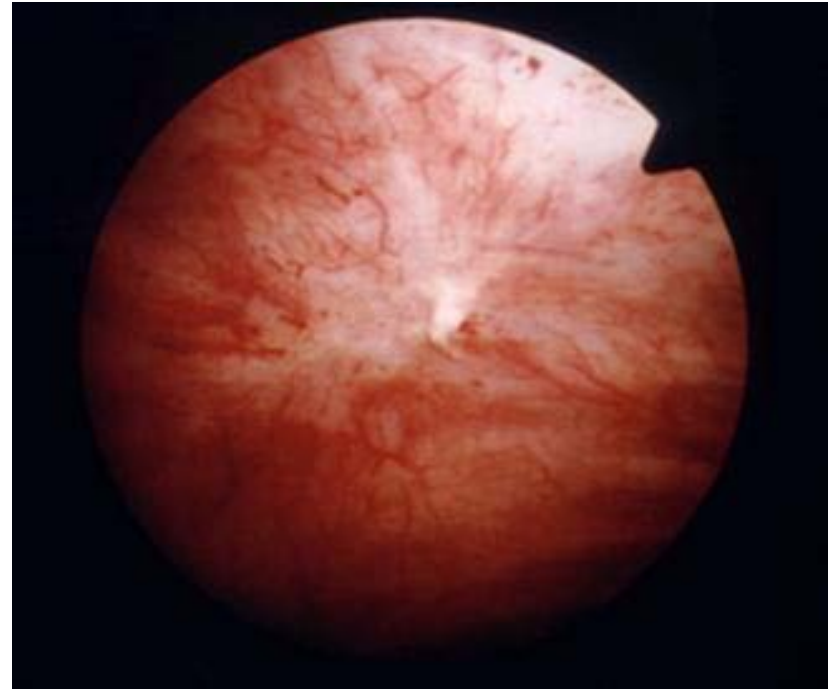
Epidemiology



- From 40,000 to 60,000 cases per year are reported in USA, but nobody knows how many have it. Actual incidence may be at least 5 times greater.
- 90 % of IC cases are women.
- 65 % of IC cases are people aged 20 to 40. The average age of onset is 40, with 25% of patients under the age of 30.
- 50% of IC patients have pain while riding a car.
- No evidence of genetic transfer.
- 63 % of IC patients are unable to work fulltime.
- Quality of life of IC patients is worse than patients experiencing renal failure and undergoing dialysis.
- The patient's life is dominated by the question: *where am I going to find the next toilet ?*

IC: Two Types

- classic IC with Hunner's ulcer
- non-ulcerative IC



Early Non-ulcerative IC



- *It is the most common type of IC.*
- *Glomerulation (strawberry like hemorrhages) can be seen in the bladder wall.*
- *Bladder capacity is normal, near normal or increased.*
- *Occasionally, stellate scars that crack and bleed, or mucosal fissures, may be seen.*
- *No granulation tissue is found.*

Classic ulcerative IC



- *It affects middle age to older women*
- *(5-10 % of IC patients).*
- *Bladder capacity is low.*
- *Cracks scars and star shaped sores (Hunner's ulcers) may bleed.*
- *Granulation tissue is present in most of the cases.*

Interstitial Cystitis: a bladder disorder



- *About the bladder:*
- A triangle-shaped chamber in the lower abdomen.
- Like a balloon with elastic walls which relax and expand to store urine, contract and flatten to empty urine.
- Tissues of the bladder are isolated from urine and toxic substances by a coating that prevent bacteria and crystals from attaching and growing on the bladder wall.

Interstitial Cystitis: a bladder disorder



About people with IC

- Have inflamed or irritated bladder wall.
- Inflammation can lead to:
 - *scarring and stiffening*
 - *decreased bladder capacity*
 - *glomerulations (pin point bleeding)*
 - *Hunner's ulcers in the bladder lining*

Causes of IC



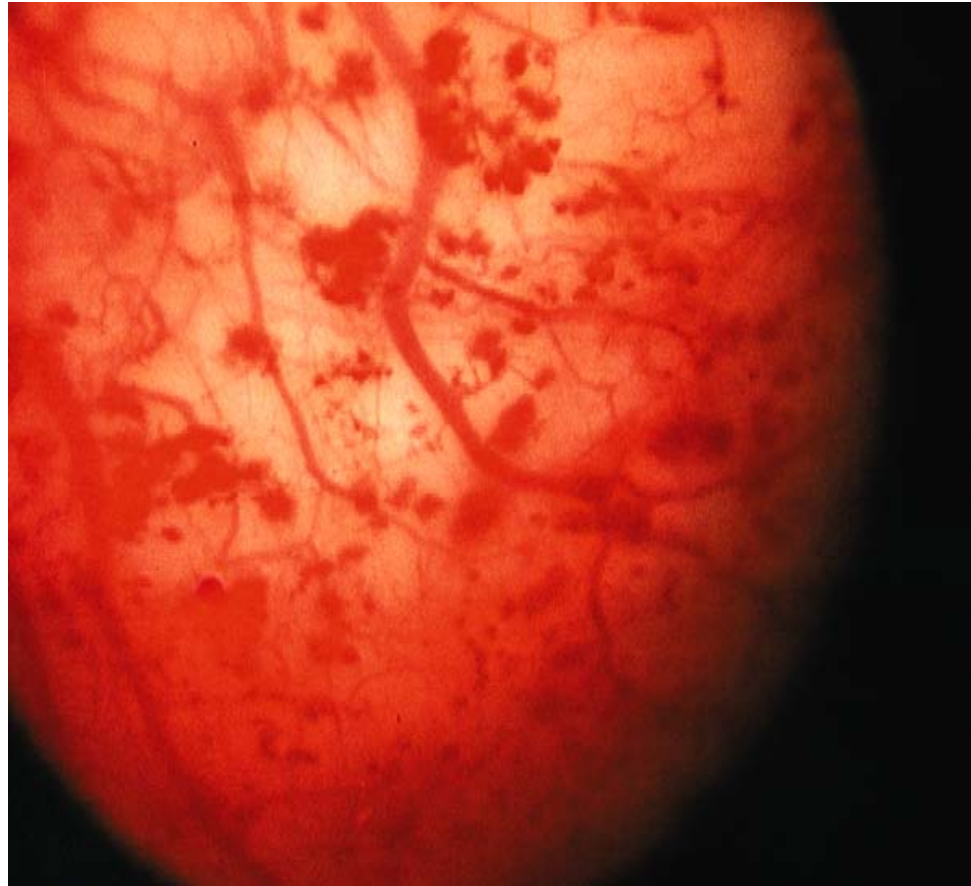
- **It is a real physical problem, not a result symptom or sign of an emotional problem.**
- **The lining of the bladder called glycocalix made up primarily of mucins and GAGs is “leaky”.**
- **Infections may have started an auto-immune response against the bladder.**
- **Infective organisms may be present in bladder cells (not detectable through routine tests).**

Disfunctional bladder epithelium

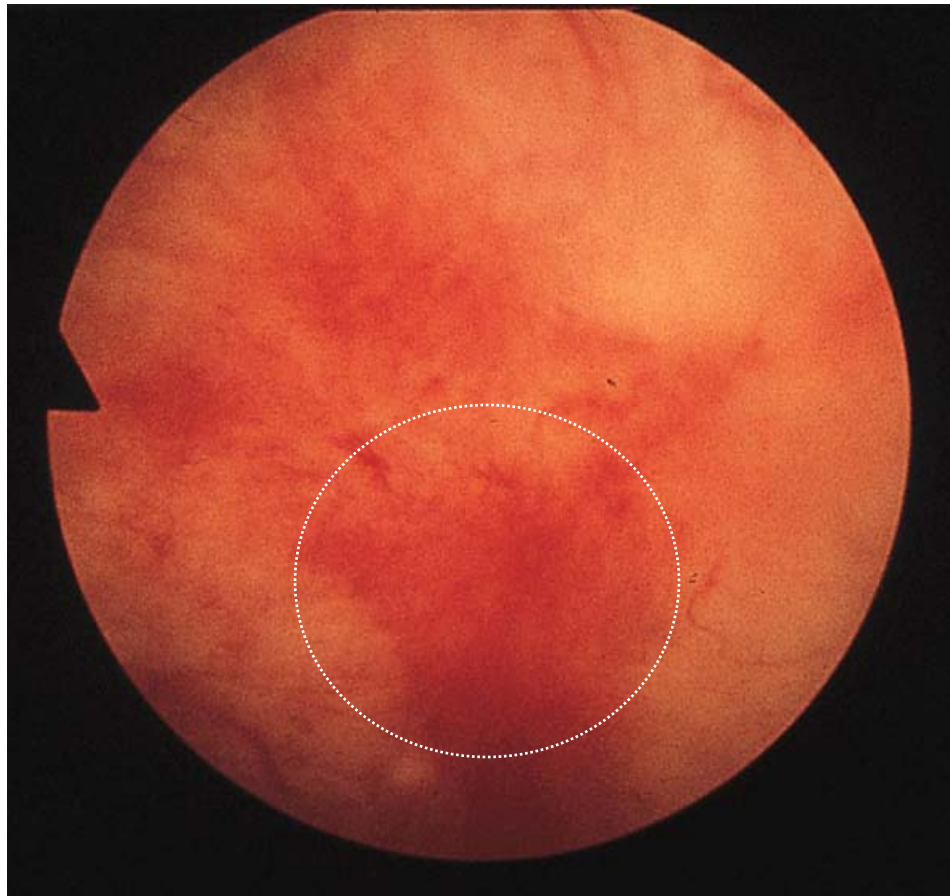


- **Bladder surface GAG maintains the epithelial permeability barrier between the bladder wall and urine.**
- **Negatively charged polysaccharides groups have high affinity for binding water molecules.**
- **This hydrated surface layer is the barrier between bladder wall tissues and the urine which prevents the urinary solutes such as Urea and Calcium from damaging bladder cells. A defective GAG layer would subject bladder cells to harmful solutes.**

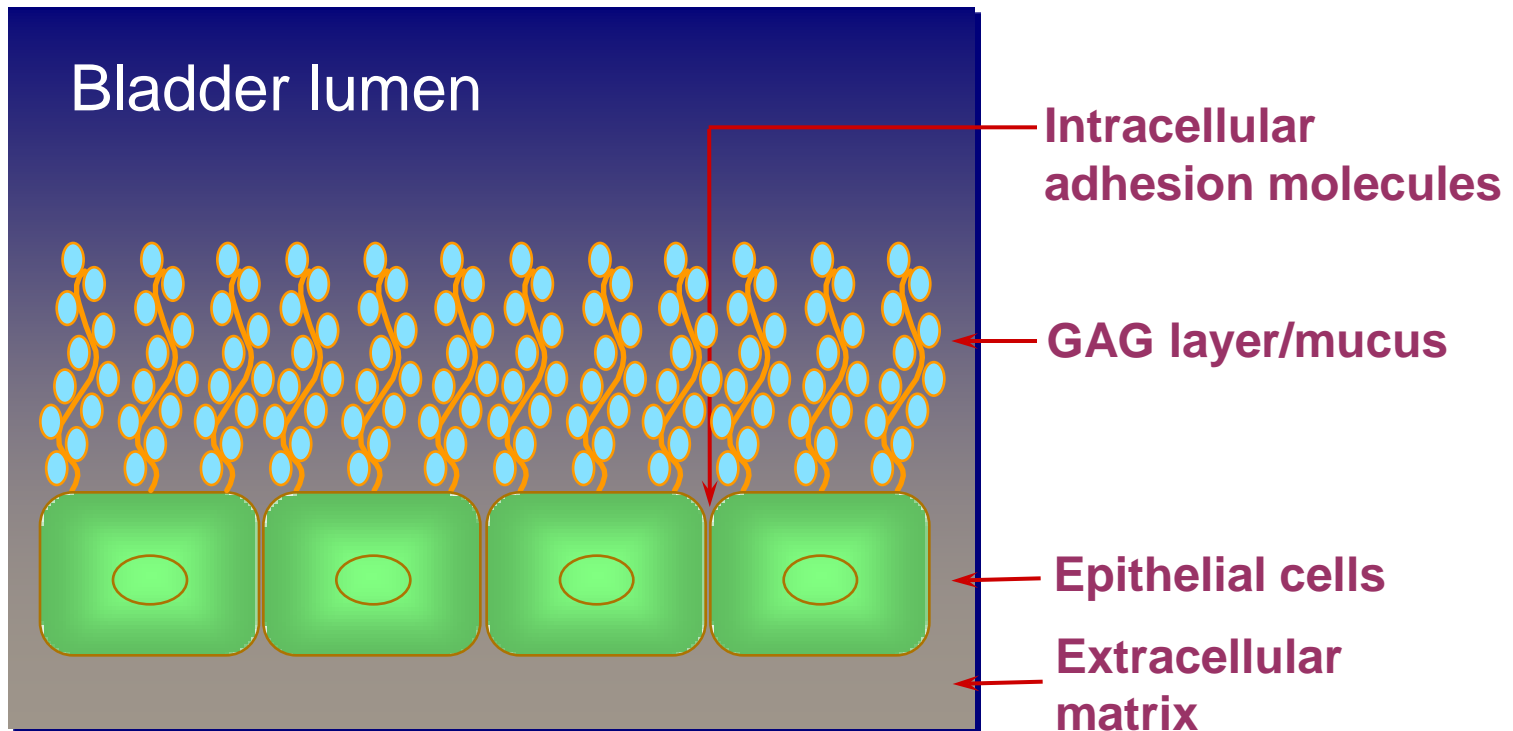
Glomerulations as Seen on Cystoscopy



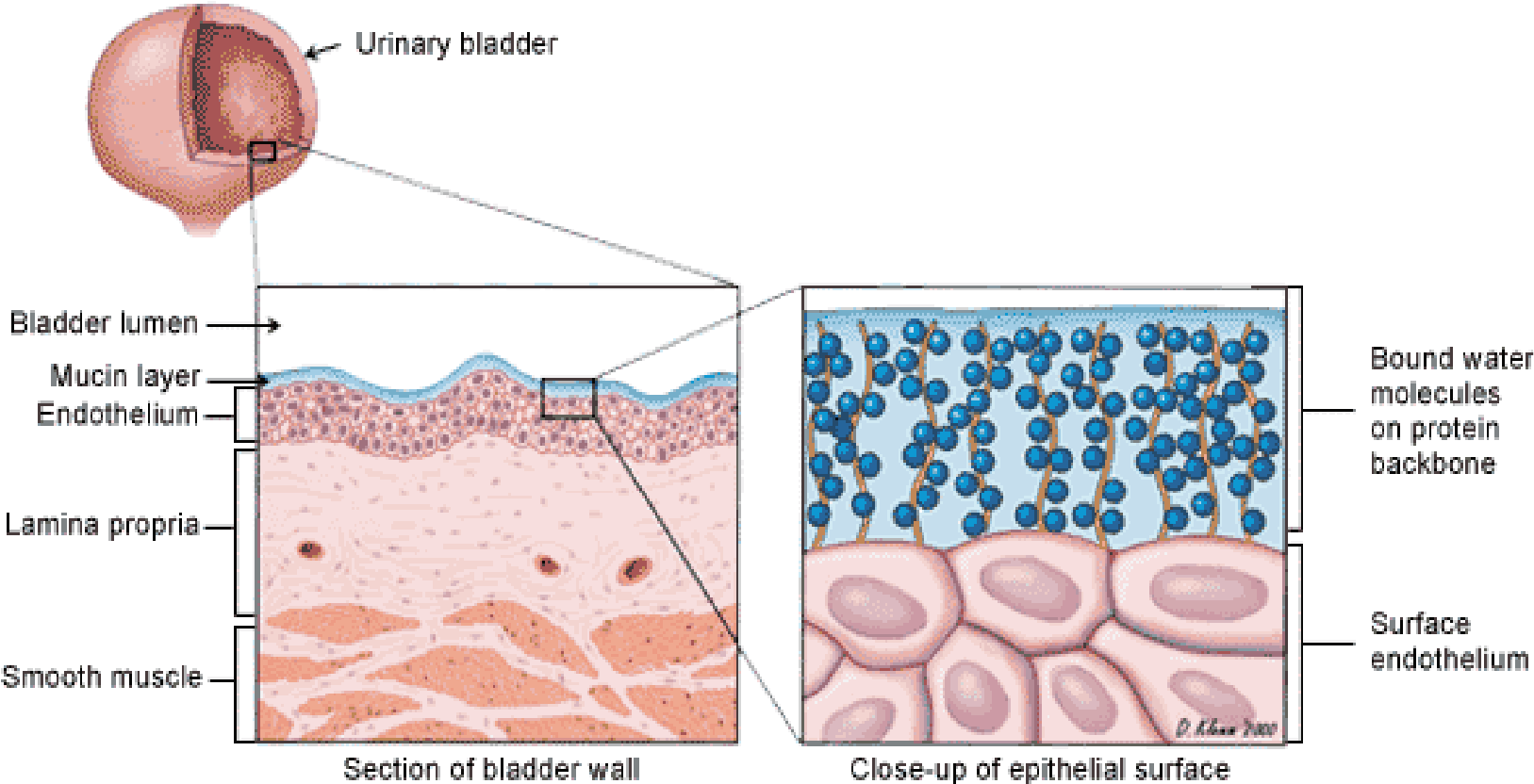
Hunner's Ulcer



The Normal Bladder



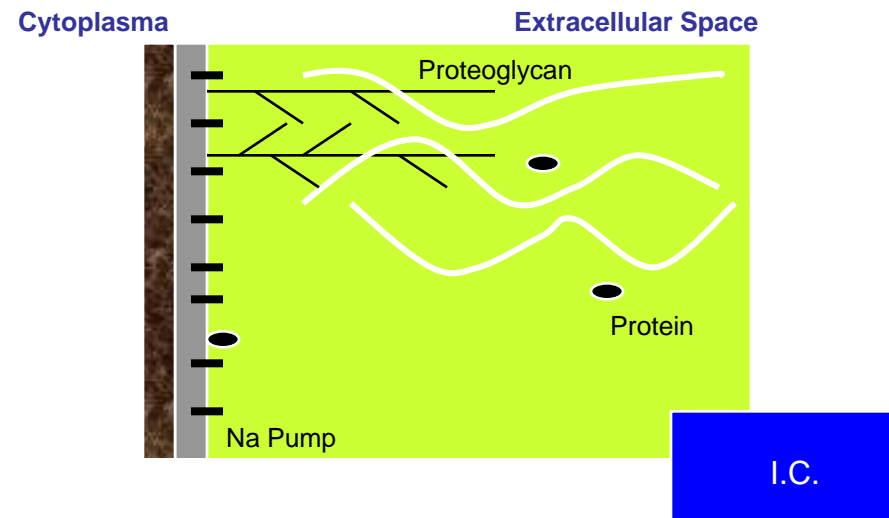
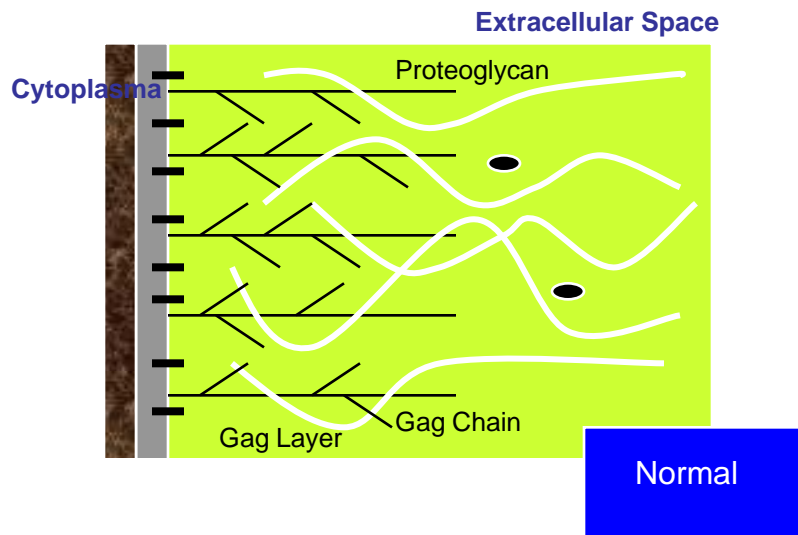
BLADDER WALL STRUCTURE



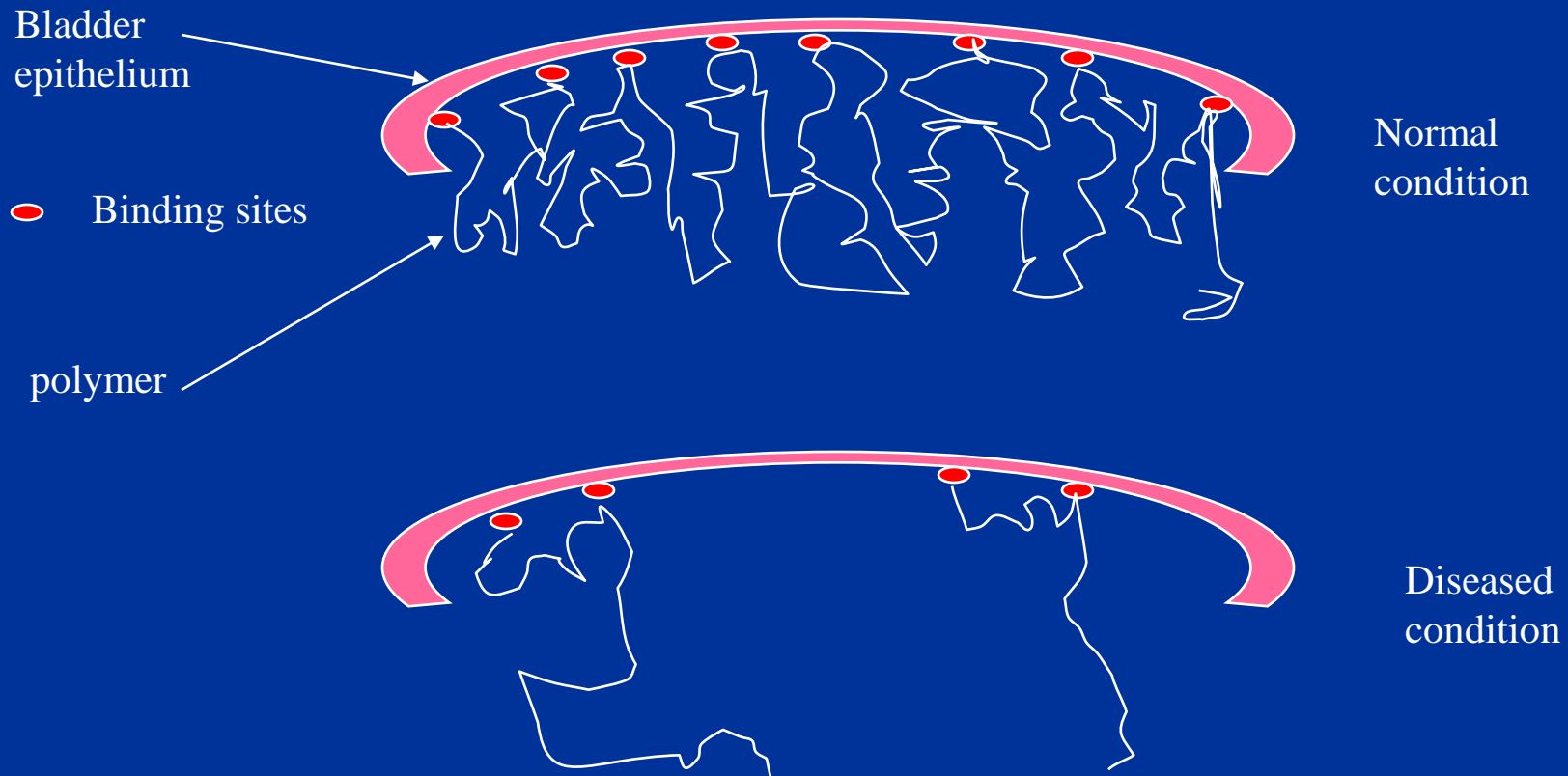
Small blue circles represent bound water molecules, and wavy lines represent the protein Backbone. (Julius F. Metts MD, American Family Physisican, vol. 64 no 7 (2001).

Disfunctional bladder epithelium

The bladder mucosa is lined by a layer of GAGs :
Hyaluronic Acid, Heparine, Chondroitin Sulphate,
Dermatin Sulphate and Keratin Sulphate.

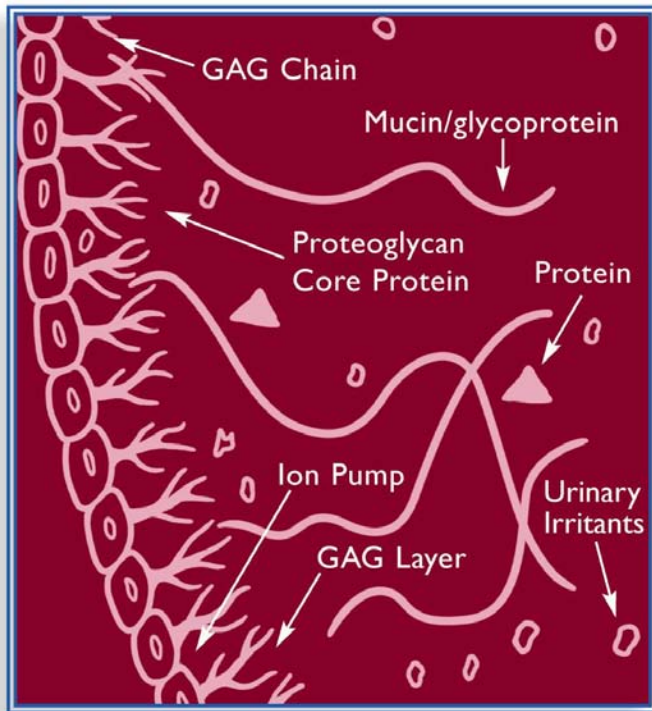


Polymer Connection to the endothelial wall

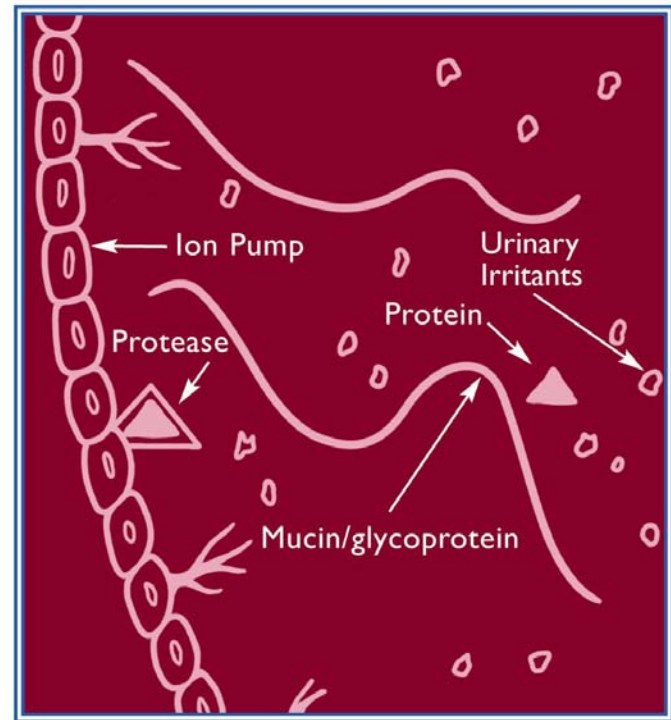


* The shorter the polymer, the lesser the number of binding sites, implying the possibility that the polymer will lose its attachment to the endothelium.

The GAG Layer

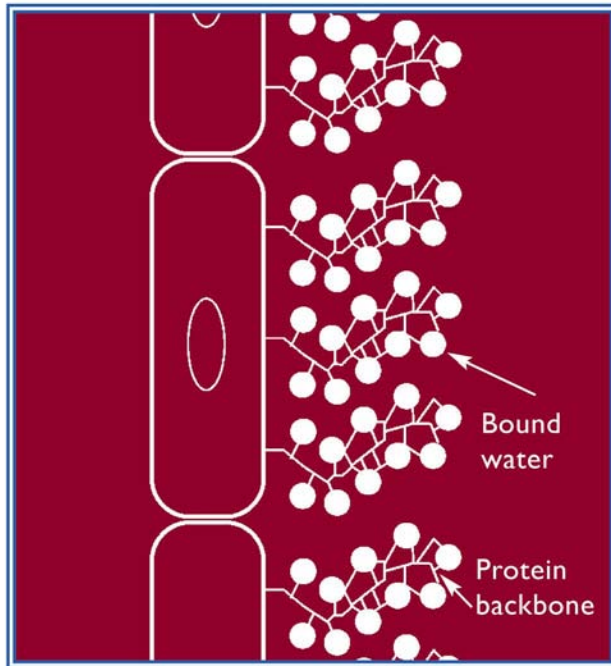


Normal GAG



Leaky GAG

Biofilm Layer

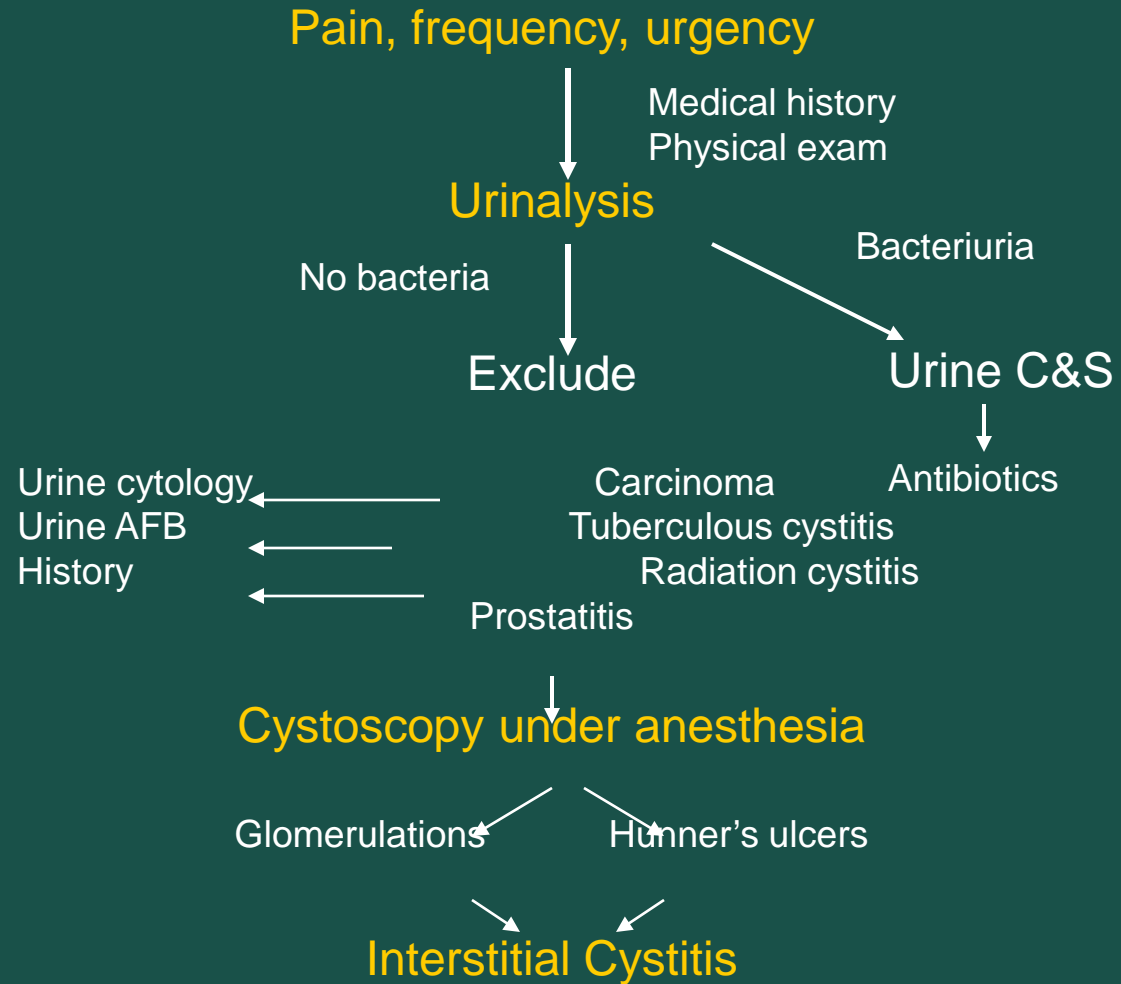


Diagnosis



- Presence of urgency, frequency or pelvic/bladder pain
- Sterile and cytologically negative urine
- Cystoscopic evidence (under anaesthesia) of bladder wall inflammation and glomerulations or Hunner's ulcers.
- Absence of other diseases that may cause the symptoms.

Diagnosis Algorithm



Treatment



- **Bladder distension**
- **Bladder instillation**
- **Oral drugs**
- **TENS (Transcutaneous Electrical Nerve Stimulation)**
- **Diet, No-Smoking, Exercise**
- **Bladder training**
- **Surgery**

Treatment



Bladder distension

Is often thought to be one of the first treatment attempt.

Treatment may increase bladder capacity and interfere with pain signals transmitted by nerves in the bladder.

Treatment



Bladder instillation-1

The only drug approved by the USA FDA is the methylsulphoxide (DMSO, RIMSO-50).

Treatments are given every week or 2 for 6 to 8 weeks and repeated if needed.

Improvement of symptoms are seen after 3 to 4 weeks.

DMSO work reducing inflammation and blocking pain.

Side effect is garlic-like taste and odour.

Treatment



Bladder instillation- 2

Other drugs used:

- ◆ Silver nitrate
- ◆ Sodium oxychloroxene (Clorpactin)
- ◆ Heparin
- ◆ Pentosan polysulphate (Elmiron)

The first two treatments are very painful and must be done under general anaesthesia

Oral Drugs



- **Therapeutic Class**
 - anti-inflammatory drugs
 - antispasmodics and anticholinergics (i.e. oxybutynin, Tolterodine)
 - anticonvulsants (i.e. gabapentin, Neurontin®)
 - histamine-receptor antagonists (H1 and H2 receptors)
 - painkillers
 - pentosan polysulfate sodium (Elmiron® in US, in Italy as Fibrase® and in Germany as SP54®.)
 - tricyclic antidepressants (amitriptyline, imipramine, desipramine and nortriptyline)

ELMIRON (Pentosan polysulphate sodium)



It is the first drug approved by FDA for IC.

It may repair leaks in the bladder lining.

The dosage of ELMIRON is 100 mg 3 times a day.

The urinary frequency decrease takes 6-9 months and IC pain may disappear not before 2 to 4 months but only a minority of patients may benefit (The Medical Letter June 6/97).

Patients must continue therapy for at least 6 months to obtain a relieve of symptoms.

Cystistat

About SH

Physicochemical properties.

SH is a naturally occurring linear polysaccharide with distinct rheological and physicochemical properties.

It is not associated with a protein core like in the case of proteoglycan and is thus classified as a glycosaminoglycan (GAG).

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About SH

Where is it found ?

SH is present in the extracellular matrix of many mammals.

Some strains of streptococcus produce SH as extracellular component of the capsule.

In man SH is found mainly in the vitreous, in the articular matrix, in the umbilical cord and in the cardiac valves.

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About SH

SH Localisation

in NATURE

in MAN

Mammalians

Dermis

Bacteria

Vitreous

Joint matrix

Umbilical cord

Heart

Cystistat

About SH

SH Role in IC

It has been hypothesised that IC patients may have a defect in the epithelial permeability barrier of the bladder surface. GAG layer is believed to provide a protection against irritative components of urine,(such as micro-organisms carcinogens, crystals and other agents), which may otherwise penetrate into the more sensitive layer of the bladder wall.

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About SH

Rationale

The development of protective bladder coatings is essential to create a barrier. Glycosaminoglycan layer constitute an ideal epithelial permeability coat of which IC patients may be deficient and which may help to reduce irritations.

Cystistat



About
CYSTISTAT

What is it ?

Cystistat is a new form of treatment for IC where the main active ingredient is SH, a natural occurring polysaccharide.

Cystistat



About
CYSTISTAT

What is it ?

It is a new treatment for IC which contains SH. It is presented in a 50 ml vial containing 40 mg SH. Cystistat was developed at Queen's University in Kingston, Ontario and was introduced to the Canadian market in 1995, the first country in the world to market Cystistat.

Cystistat

About
CYSTISTAT

Dosage and administration

Initial treatment of 4 weekly instillations followed by instillations given every month for 5-6 months. (It should be noted that 5 or 6 treatments are often required before it is known if the treatment is effective)

Thereafter if significant relief has been obtained, the interval between treatments can be increased to 6, 8 and 12 weeks on a gradual basis. As soon as there is an indication of recurrence the patient should have another treatment.

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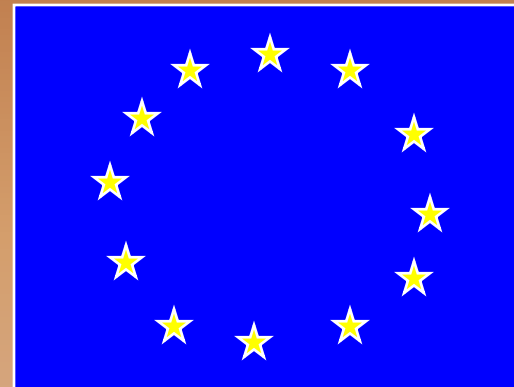
About
CYSTISTAT

Regulatory Status in Europe

Registered as Class II a Medical Device by
AMTAC notified body in the UK .

CE mark

CE₀₄₇₃



Analysis of two Cystistat Studies



Alvaro Morales *et al.*, Kingston, ON

and

Tage Hald *et al.*, Herlev, Denmark

Protocol



- ◆ Refractory Interstitial Cystitis (IC)
- ◆ Two open-label, noncontrolled studies
- ◆ Intravesical Cystistat weekly for four weeks —
then monthly
- ◆ Evaluation after fourth and sixth treatment

Demographics



- 44 female patients
 - Canada: 25
 - Denmark: 19
- All previously treated for IC
- Mean age: 57 years (28-81)
- Mean duration of pain: 71 months (9-300)

Evaluated Outcomes



- Meta-analysed outcomes
 - Pain
 - Awake-time urinary frequency
 - Nocturia (sleep-time urinary frequency)
- Other outcomes (Canada only)
 - Clinical symptoms
 - Urinary urgency

Meta-Analysis Results

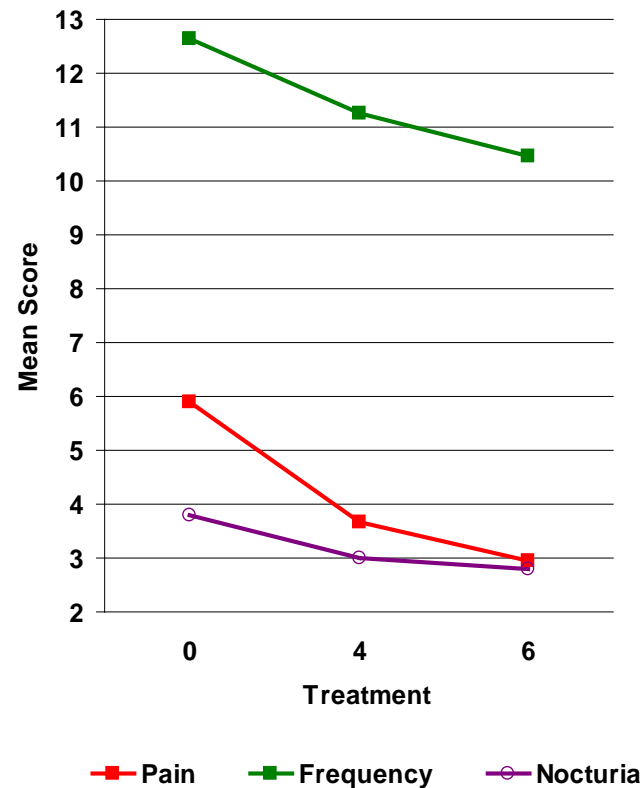
After Six Treatments

- ◆ 93% of patients (41/44) demonstrated an improvements in measured outcomes
- ◆ All measured outcomes were significantly improved

☐ Pain ($p < 0.001$)

☐ Day Frequency ($p < 0.1$)

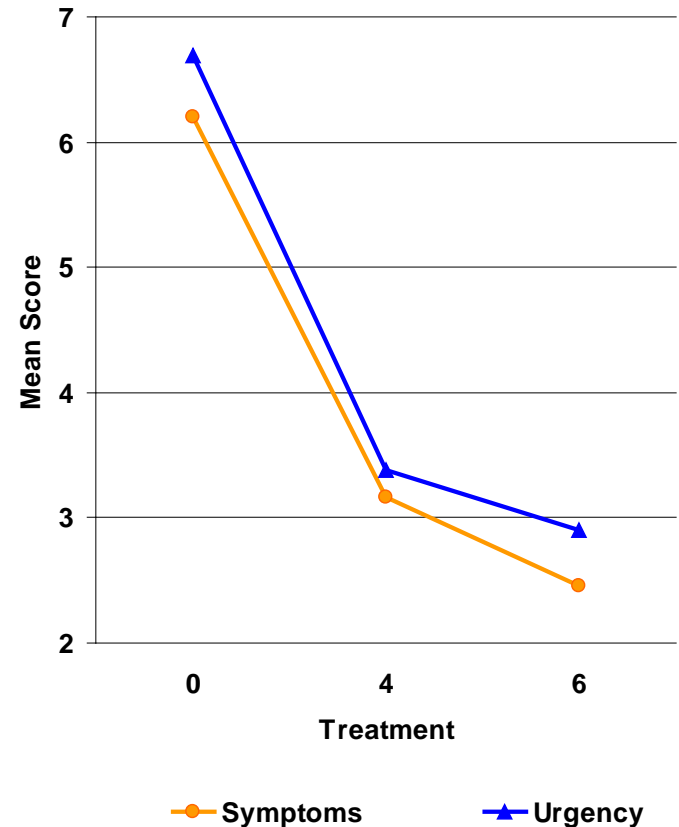
☐ Nocturia ($p < 0.1$)



Other Outcome Results

After Six Treatments

- The Kingston (Morales) study also evaluated Symptoms and Urgency (25 patients)
- These had significantly improved after four treatments
 - **Symptoms** ($p < 0.001$)
 - **Urgency** ($p < 0.001$)



Overall Results After Six Treatments

Effects of Cystistat® on Symptoms Associated with Interstitial Cystitis — Mean Value (SD)

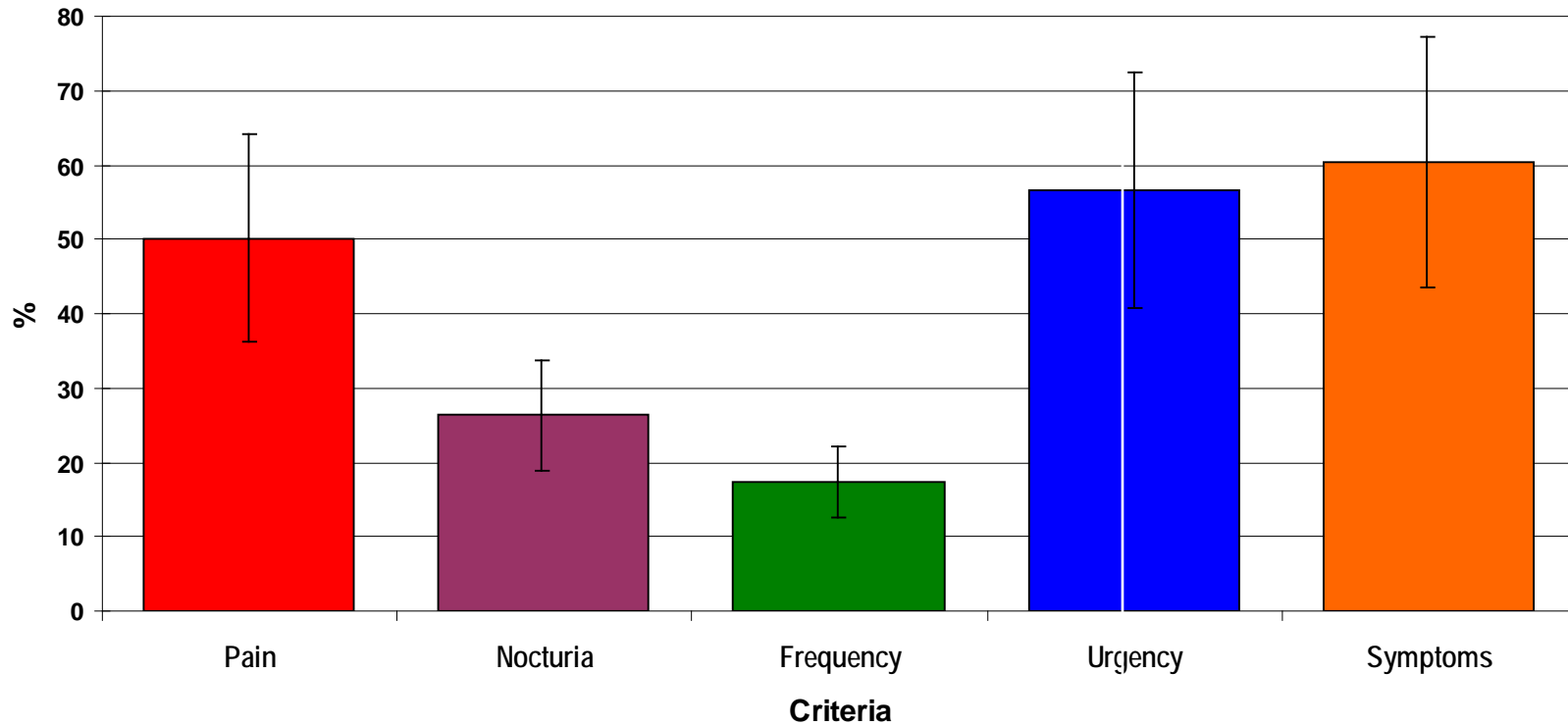
Evaluated Parameter	n	Pretreatment	Following Treatment 4	Following Treatment 6
Pain (10cm VAS)*	44	5.88 (2.47)	3.65 (2.54) ^a	2.89 (2.63)^a
Daytime Frequency*	37	12.63 (4.72)	11.24 (4.78)	10.44 (4.57)^b
Nocturia*	37	3.87 (2.54)	3.05 (2.38)	2.88 (2.24)^b
Clinical Symptoms (0-15)**	25	6.20 (1.50)	3.16 (1.55) ^a	2.46 (1.56)^a
Urinary Urgency (10cm VAS)**	25	6.69 (1.64)	3.38 (2.36) ^a	2.90 (2.95)^a

Superscripts indicate p value: ^a p<0.001 ^b p<0.1 (ANOVA, alpha=0.01)

* Morales and Hald studies. ** Morales (Canada) study only.

Overall Results After Six Treatments

Morales/Hald IC Studies
Change% After Six Cystistat[®] Treatments





Cystistat

Other studies

Existing Clinical Evidences

1. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. *Morales et al, J. Urol 1996*
2. Results of treatment of refractory interstitial cystitis with intravesical hyaluronic acid. *Porru et al, Urol Int 1997*
3. Cystistat for the treatment of IC. An open uncontrolled study. *Kallestrup et al. Int Continence Society, Denver, 1999*
4. Our experience in the treatment of IC. *Sommariva et al, 2001*
5. Effect of sodium hyaluronate bladder irrigation. *Searles et al, BJU 2001*
6. Cystistat for the treatment of IC: a 3 year follow-up study. *Nordling et al, Urology 2001*
7. Preliminary results from the use of HA as a preventative agent for recurrent cystitis in female. *Constatinides et al, MUA Congress 2001, BJU International 2004*

Existing Clinical Evidences II

8. Effect of diagnostic hydrodistension and four intravesical hyaluronic acid instillations on bladder ICAM-1 intensity and association of ICAM-1 intensity with clinical response in patients with interstitial cystitis *Leppilahti et al, Urol 2002*
9. Is a Maximal Bladder Capacity of >400 cc an Automatic Exclusion Criteria for Interstitial Cystitis? *Daha et al. 2002 SIU*
10. Intravesical HA for the treatment of IC. *Riedl et al. 2003 AUA*
11. HA in the prevention of radiation cystitis. *Delgado et al, ASCO 2003*
12. Prevention of UTI by bladder instillations of HA Cystistat in patients with metastatic medullar compression. *Manas et al, SIFUD 2003*

Existing Clinical Evidences III

13. *Prospective randomised controlled trial of intravesical dimethylsulphoxide (DMSO) vs Cystistat (Hyaluronic acid) in the treatment of female patients with interstitial cystitis (IC). Singh M et al, ICS 2003*
14. *Intravesical instillation of sodium hyaluronate for the treatment of recurrent non-bacterial cystitis – a multi-centre study. Prof. Y. F. Zhang et al. SUC Congress July 2004*
15. *Intravesical hyaluronic acid for the treatment of IC: an update. Riedl et al. MICA Congress Sept 2004.*
16. *Management of cystitis/non-malignant inflammatory conditions of the bladder and the use of intravesical hyaluronic acid. Riedl et al. MICA Congress Sept 2004.*
17. *Where to start for clinical trials in IC? A report on a recently concluded trial. Whitmore et al. MICA Congress Sept 2004.*
18. *Use of sodium hyaluronate in patients suffering from post-radiation cystitis. Diamantopoulos et al. ESTRO Oct 2004*

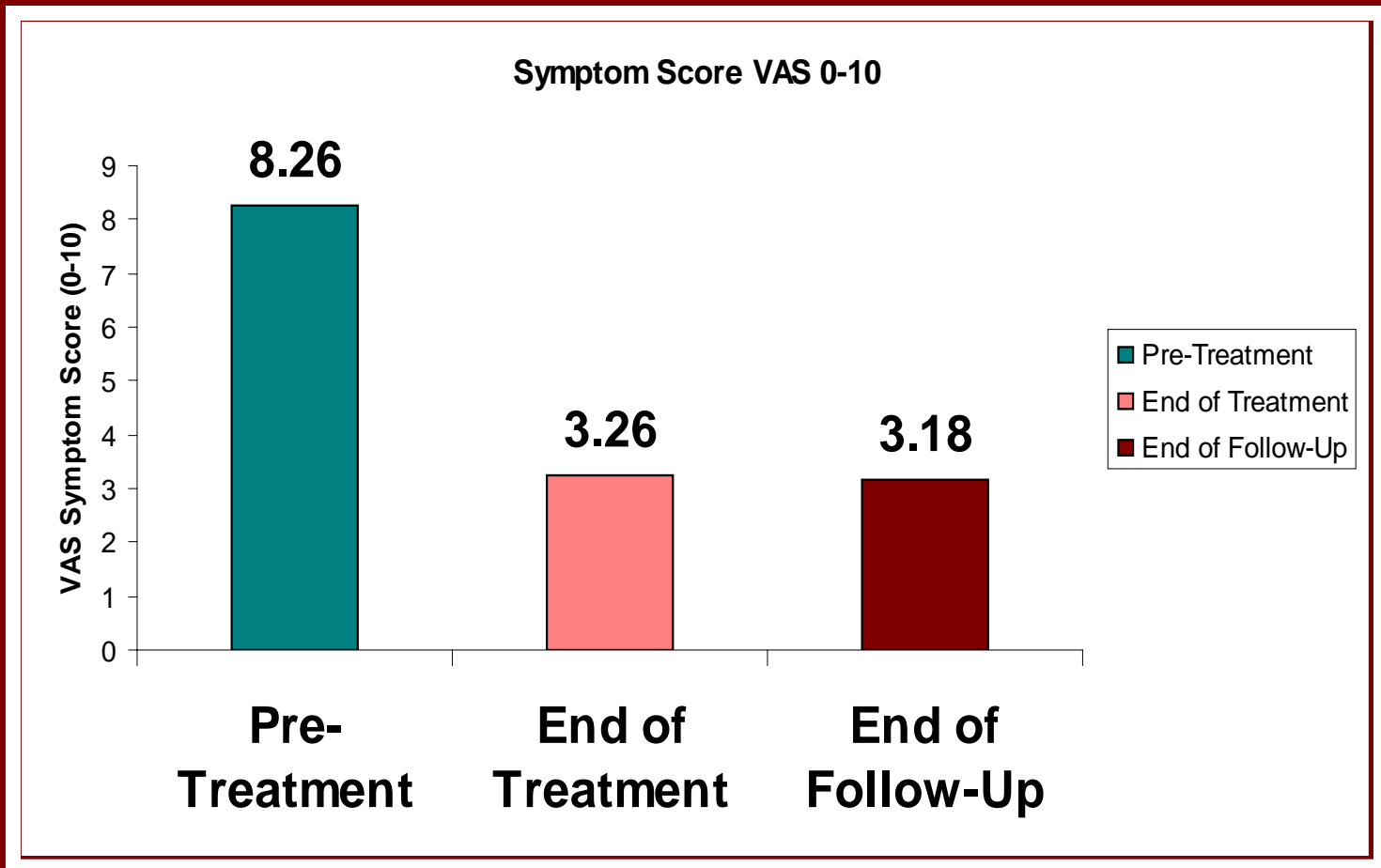
Study	Date	IND	P. No	Design	Parameter	Results	Publish / present
Morales	1996	IC	25	Open, non-comparative	Symptom score; voiding diaries;	56% at W4; 71% at W12, response maintains till W20;	J. Urology
Porru	1997	IC	10	open	Symptom scores: voiding diaries	30% response at W6, till W24; well tolerated	Int Urology
Kallstrup	1999	IC	20	open	Symptom scores; VAS; use of analgesics	↓ in pain; ↓ in frequency, ↓ in analgesic intake	ICS 1999
Sommariva	2001	IC	15	open	Symptom score, pain, bladder capacity	85.7% ↓ in pain; symptoms ↓; bladder capacity ↑	Uro-dinamica 2001

Study	Date	IND	P. No	Design	Evaluation Parameter	Results	Publish / present
Searles	2001	Neurogenic dysfunction	7	open	Pain, symptoms	Immediate pain relief	BJU
Nordling	2001	IC	20	Prospective unblinded, open	Voiding diary; pain VAS	substantial reduce in pain; Improvement in frequency; 20% recovered; no side effects	Urology
Leppilahti	2001	IC	11	Open label	Pain VAS, voiding diary, ICAM score index	Pain ↓ by 75% after 2 w; effect may lasts till 8 months; Micturition volume ↑ 65%	Urology

Study	Date	IND	No patient	Design	Evaluation Parameter	Results	Publish / present
Constanti-nides	2001	RBC	40	open	No of UTI and time to recurrence	70% free of RC; 92.4% ↓ in no of RC; 5 folds ↑ T to RC; good safety profile	BJU 2004
Daha	2002	IC	28	Open label, comparative	Cmax Test;	Complete remission in 13/15 of patients with Cmax>400ml ; 8/10 with Cmax<400ml	SIU 2002

Study	Date	IND	No patient	Design	Evaluation Parameter	Results	Publish / present
Delegado	2003	RIC	90	Two arms: UC vs UC+HA	Toxicity index RTOG/EO RTC, GPS score; UTI tracking	46% ↓ in toxicity grade; ↓ UTI; ↑ QOL	ASCO 2003
Manas	2003	UTI prevention	71	Two arms: UC vs UC+HA	UTI tracking	14% in HA group, 76% in UC group	SIFUD 2003
Riedl	2003	IC	70	retrospective questionnaire based	KCI Cmax test; Symptom VAS	85.7% of patient reported ↑ ≥2 on VAS; 82% ↑ QOL; 87% continue HA treatment no 05	AUA 2003

Intravesical Cystistat [®] in the treatment of IC -- *Dr. Riedl et al 2003 AUA*



**Intravesical Cystistat [®] in the treatment of
IC -- *Dr. Riedl et al 2003 AUA***

VAS improved ≥ 2	85.7%
VAS improved < 2	4.3%
Unchanged	10.0%

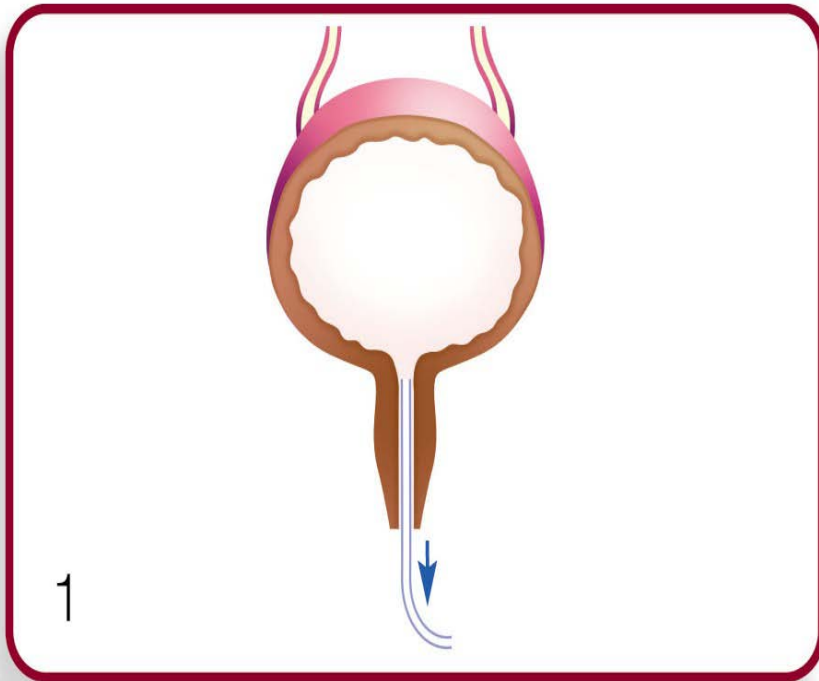
Intravesical Cystistat ® in the treatment of IC -- *Dr. Riedl et al 2003 AUA*

- *Screened patients have a > 80% chance of significant symptom remission with hyaluronic acid instillations.***
- *Improvement is maintained over at least six months.***
- *In about 1/3 of patients, continuation of instillations may be necessary to maintain the therapeutic effect.***

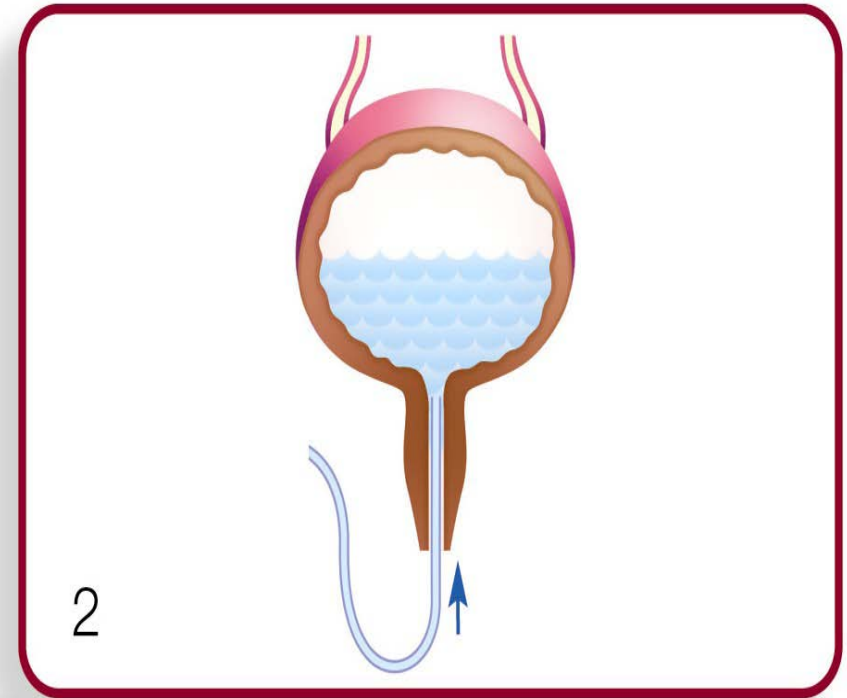
Comparative Cystometry Test (CCT) Identifying a defective GAG layer: Riedl's Test

A defective GAG layer is indicated by a 30% or greater reduction in bladder capacity with 0.2 M potassium chloride compared to saline.

Comparative Cystometry Test (CCT)

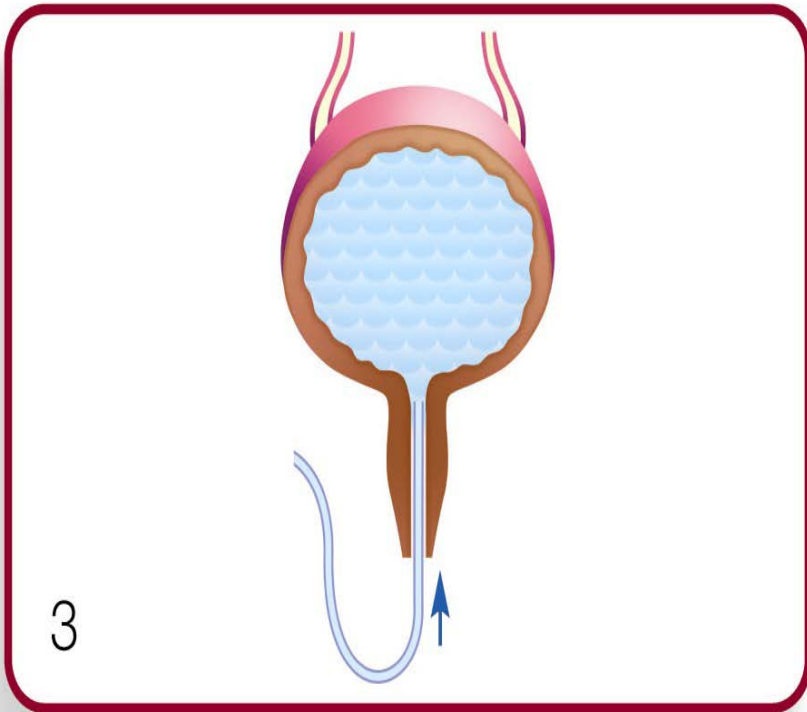


- Explain procedure, obtain patient consent
- Insert a 14F bladder transurethral catheter
- Empty residual bladder volume

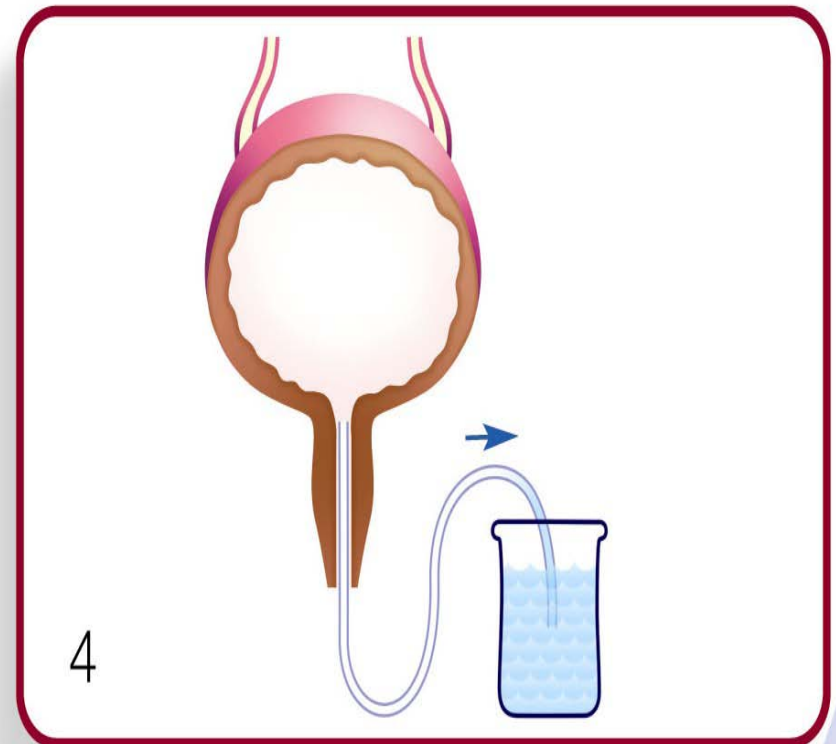


- Fill bladder with sterile room-temperature normal saline at a rate of 50 ml/min using infusion pump or gravity drainage

Comparative Cystometry Test (CCT)



- Patient reports first strong urge to void
- Continue filling until patient says, 'Stop filling'



- Drain the bladder and measure the volume of saline

Comparative Cystometry Test (CCT)



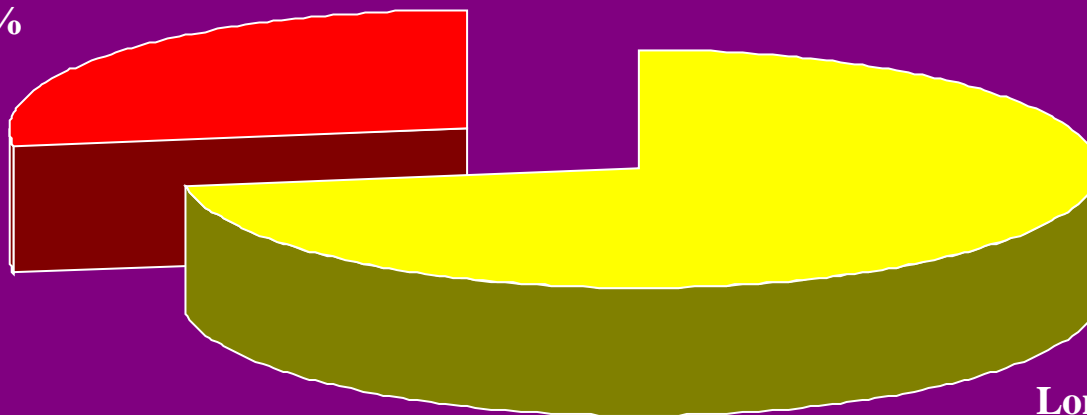
$$\frac{\text{Volume saline} - \text{Volume KCl}}{\text{Volume saline}} \times 100 = \% \text{ Reduction}$$

- Repeat the procedure using 0.2M sterile potassium chloride (ensuring filling lines are free of saline)

- Calculate the % difference in maximal bladder capacity

Effect of diagnostic hydrodistension and four intravesical hyaluronic acid instillations on bladder ICAM-1 intensity and association of ICAM-1 intensity with clinical response in patients with interstitial cystitis *Leppilahti et al, Urol 60:46-51, 2002*

non-responder
27%



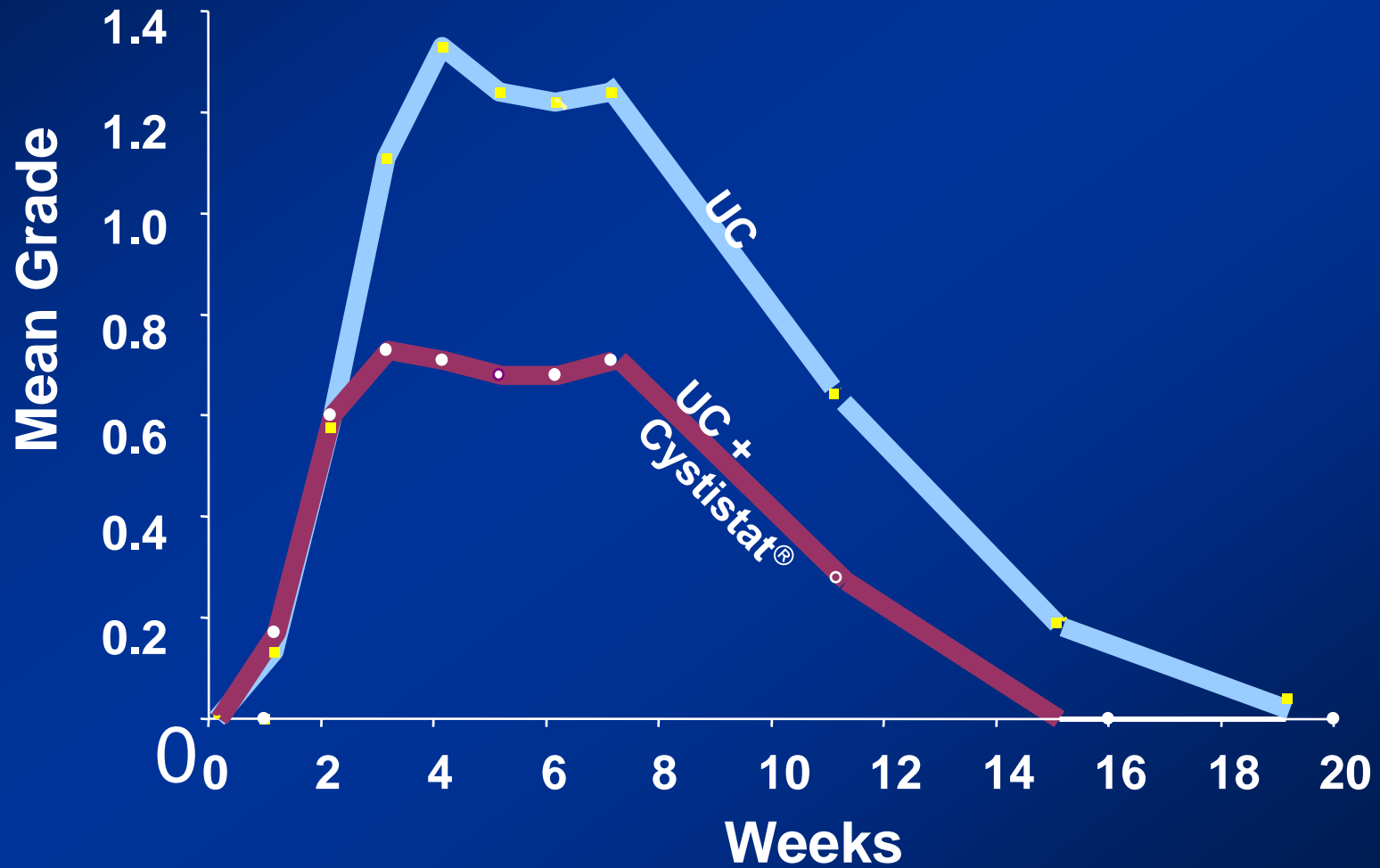
Long/short-
term responder
73%

- *Two weeks after the final instillation, pain was reduced by 75% in the responders according to VAS.*
- *Long term responders were not in pain even after 8 months.*
- *Two weeks after the final instillation, the mean micturition volumes were increased by 65% in the long-term responders and by 21% in short-term responders.*

- - Leppilahti et al, Urol 60:46-51, 2002

CYSTISTAT[®] REDUCES RADIOTHERAPY TOXICITY

Delgado et al, ASCO 2003



Key Results

- Average Radiation Toxicity Grade**

	UC	UC + Cystistat [®]	p-value [1]
Week 4	1.33	0.71	p<0.0001
End Radiotherapy	1.24	0.71	p<0.0001

- Radiation toxicity grade was decreased by 46% in the Cystistat[®] group at the end of the treatment.**
- At the end of the treatment (week 7), Cystistat[®] treated patients experienced a maximum toxicity of Grade 1 whereas 24.4% of UC patients were still experiencing toxicity of Grade 2 (p<0.0001).**
- At the two month follow up (week 15), none of the patients in the UC+Cystistat[®] group were experiencing radiation-induced toxicity whereas 20% of the patients in the UC group were experiencing toxicity of Grade 1 (p=0.0025).**
- One UTI was reported in the UC+Cystistat[®] group (2.2%) versus 4 (8.8%) in the UC group.**
- No Cystistat[®]-related adverse events were reported.**
- The radiotherapy schedule had to be delayed for 2 (4.4%) patients in the UC group versus none in the UC+Cystistat[®] group.**

CYSTISTAT® REDUCES RADIOTHERAPY TOXICITY

Delgado et al, ASCO 2003

Results:

Weekly bladder instillations of HA (Cystistat®) protect the bladder, decrease radiation induced toxicity, risk of infection and enhance the quality of life of patients treated with pelvic radiotherapy.

*Preliminary Results on the Use of HA Intravesical Instillations
for the Preventive Treatment of Women with Recurrent
Bacterial Cystitis*

-- Constantinides et al

**Median time to recurrence in pre and post hyaluronic
acid treatment**

Pre-treatment	Post-treatment	p value
96 days	498 days	<0.0001

RESULTS:

- **70% (28/40) of patients were free of recurrences at the end of the follow-up (mean = 12.4 months)**
- **92.4% decrease in the number of recurrences per year was observed (0.33 versus 4.32 pre-treatment)**
- **5-fold increase of the time to recurrence (498 days versus 96 before the treatment)**
- **Number of pre-treatment UTI is a strong predictor of recurrence**
- **Good safety profile**
- **Prophylactic intravesical administration of hyaluronic acid significantly increased the time to relapse and reduced the recurrence rate of bacterial infections in women with RBC.**

SUMMARY

⌘ *In total, we have 18 published studies on Cystistat ® involving 447 patients.*

☒ *219 on IC*

☒ *110 on RIC (two arms)*

☒ *40 on RBC*

☒ *7 on neurogenic bladder*

☒ *71 on UTI of AMMC (two arms)*

⌘ *There are 3 comparative studies.*

⌘ *Ongoing studies: CISTIC (110 patients), RBC (60 patients), DMSO vs HA (30 patients).*

In the Treatment of IC

- 1. 12 studies (with 219 patients) confirmed that Cystistat ® is effective in relief of pain and reduction of frequency.***
- 2. 11 studies (with 209 patients) showed partial or complete response rate of Cystistat ® at 71% - 85.7%.***
- 3. All the 18 studies showed Cystistat ® is very well tolerated.***
- 4. Studies proved Cystistat ® can increase the bladder capacity of IC patient, reduce intake of analgesics, and increase QOL.***

Other Indications

- 1. Cystistat® is effective in the treatment or prevention of other symptoms / diseases such as,**
 - a) pain-relieving for neurogenic bladder dysfunction patients;**
 - b) prevention of UTI for AMMC patients,**
 - c) prevention of RBC.**
- 2. Cystistat® is effective in protecting GAG of bladder from damage caused by radiation therapy.**



Cystistat Distribution Network

Europe

Austria

Cyprus¹

France

Germany

Greece

Ireland

Italy

Netherlands

Portugal¹

Scandinavia

Spain

Switzerland

Turkey²

U.K.

¹ to be launched early 2005

² under registration

³ registered



Cystistat Distribution Network

Eastern Europe

Bulgaria²

Czech Republic²

Hungary²

Romania³

Slovak Republik¹

Slovenia²

Rest of the World

Brazil²

Canada

China

Mexico³

South Africa¹

South Korea

Taiwan

Singapore

¹ to be launched early 2005

² under registration

³ registered

Cystistat[®]

Bioniche Therapeutics



Cystistat[®]

Sodium hyaluronate 40mg/50mL