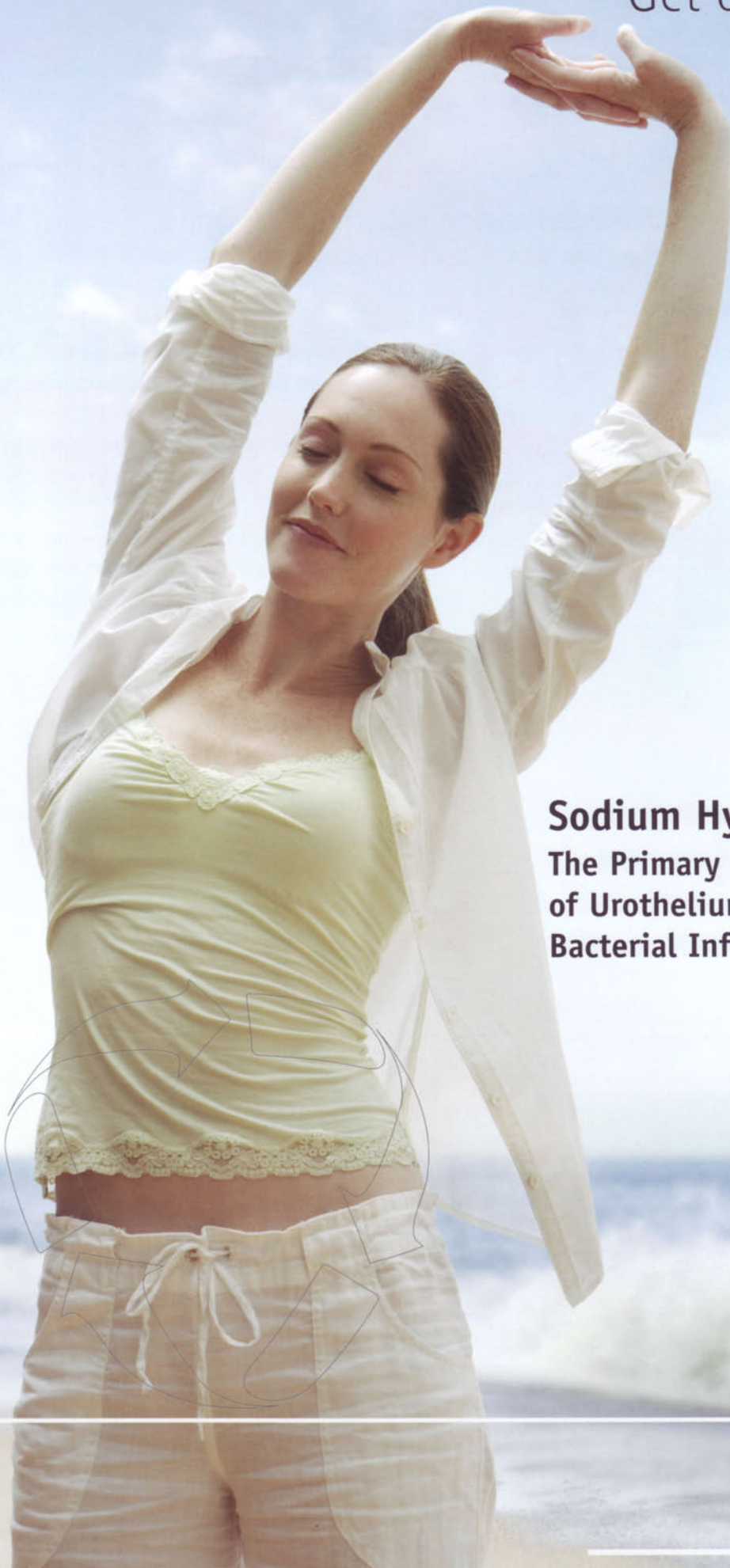


cystistat[®]

Get on with life.



Sodium Hyaluronate
The Primary Natural Defense
of Urothelium against
Bacterial Infection

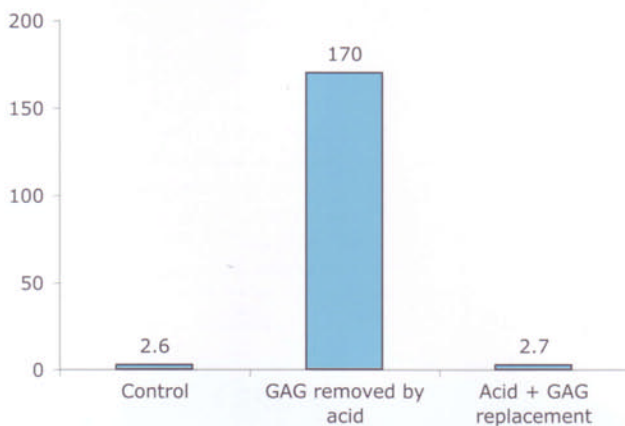
BIONICHE
PHARMA GROUP LIMITED

EXPERIMENTAL EXPERIENCES

The Anti-Adherence Factor (AAF)

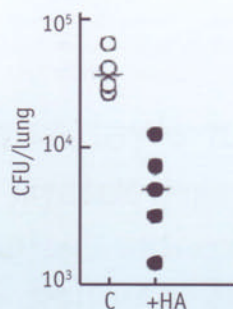
Surface GAG acts as an AAF directed against bacteria and is perhaps the most important **antibacterial defense mechanism** of the lower urinary tract.¹⁻⁸

Bacteria adherence at mucin layer



After removal of superficial GAG, there was a 50- to 60-fold rise in bacterial adherence⁸

- The presence of glycosaminoglycan (GAG) at the bladder surface markedly reduces bacterial binding.
- Exogenous GAG instillation can restore the anti-adherence activity of the surface mucin layer.



Cell surface HA is the key GAG for adherence of mycobacteria to lung epithelial cells.

HA plays an important role in the interaction between mycobacteria and lung epithelial cells.

-- Keiko Aoki et al, 2004⁹

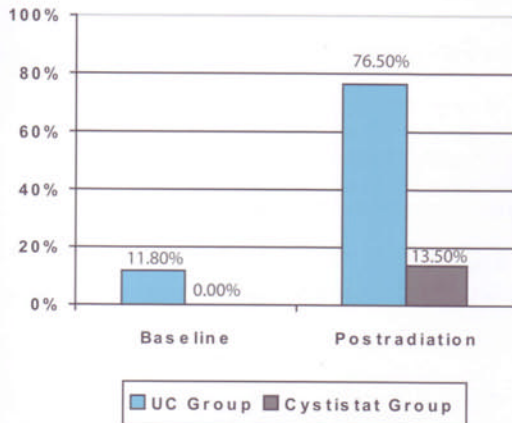
Inhibition of infection of BCG in vivo by treatment of mice with HA. C57BL/6 mice were challenged intratracheally with either 1×10^6 CFU BCG alone (C) or BCG plus 50mg of HA (+HA). All results are expressed as individual mouse data. Bars indicate averages. $p = 0.0143$ as compared between two groups by Mann-Whitney *U* test.

The Bacteriostatic Effects of Sodium Hyaluronate

- Hyaluronic acid demonstrated clear bacteriostatic effect on several most common bacterial pathogens by inhibiting bacterial growth by an average of 76.8% ($p=0.0005$). – Carlson et al, 2004¹⁰
- HA exerted bacteriostatic effects on all the bacterial strains tested, suggesting HA may prove beneficial in minimizing bacterial contamination of surgical wounds in guided tissue regeneration surgery. – Pirnazar et al, 1999¹¹

CLINICAL EXPERIENCES

Case 1: Prevention of UTI



A 5.7-fold decrease in prevalence of UTI in the group of patients receiving intravesical instillations of HA, comparing to the usual care group.¹²

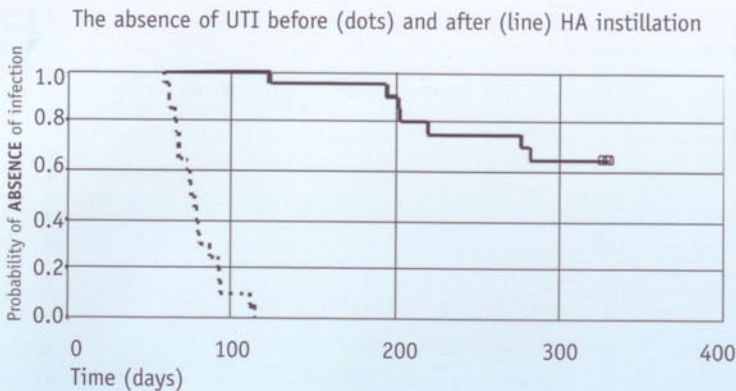
Case 2: Prevention of RBC

- 5-fold increase of the time to recurrence
- 92.4% decrease in the number of recurrences per year (0.33 vs 4.32 pretreatment).¹³

Median time to recurrence in pre and post hyaluronic acid treatment

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

Case 3: Prevention of RBC

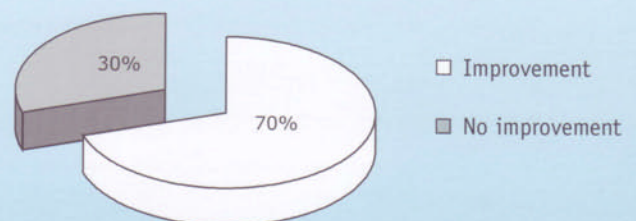


- The number of urinary tract infections per year per patient was reduced from 4.99 ± 0.92 to 0.56 ± 0.82 ($p < 0.001$)
- Time to recurrence post-HA treatment was 178.3 ± 25.5 days compared with 76.7 ± 24.6 days before treatment.¹⁴

Case 4: Urothelial healing in RBC treatment

Accelerated epithelial healing of the vesical mucosa and inhibited vesical fibrosis in 70% patients after 4 weekly instillations of sodium hyaluronate.¹⁵

HA promoting urothelial healing



Get on with life.

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PRESCRIBING INFORMATION

STERILE SODIUM HYALURONATE SOLUTION: For temporary replacement of the glycosaminoglycan (GAG) layer in the bladder.

DESCRIPTION: The glycosaminoglycan (GAG) layer on the luminal surface of the bladder wall is believed to provide a protective barrier against microorganisms, carcinogens, crystals and other agents present in the urine and has been identified as the primary defense mechanism in protecting the transitional epithelium from urinary irritants.¹ Deficiencies in this GAG layer of the bladder epithelium may destroy its barrier function and allow the adherence of bacteria, microcrystals, proteins and ions, or the movement of ionic and nonionic solute residues (i.e. urea) across the epithelium.² CYSTISTAT® has been developed to temporarily replenish the deficient GAG layer on the bladder epithelium. The active substance is a highly purified sodium salt of hyaluronic acid.

Each CYSTISTAT® vial contains: 40 mg sodium hyaluronate.

DIRECTIONS: Instill the entire volume of this solution into the bladder after any residual urine has been removed. Discard any unused portion. For best results, CYSTISTAT® should be retained in the bladder for as long as possible (a minimum of 30 minutes). There is evidence that the GAG layer of the bladder is deficient in cystitis. This deficiency contributes to the clinical symptoms² in the diseases such as interstitial cystitis,³ cystitis caused by infections, trauma, urolithiasis, urinary retention, neoplasia and radiation induced cystitis.⁴ To alleviate cystitis associated with these conditions, it is recommended that CYSTISTAT® be instilled into the bladder each week for four treatments and then monthly until symptoms resolve. The attending physician, urologist or radiologist should direct any prophylactic use of CYSTISTAT®.

PRECAUTION: Do not administer to patients with known hypersensitivity reactions. Discontinue use if adverse reactions are experienced.

WARNING: KEEP OUT OF THE REACH OF CHILDREN.

STORAGE: Store at room temperature (15-30°C). Do not freeze.

SUPPLIED: 1 x 50 mL vial of CYSTISTAT® 40 mg.

For single use only. Discard after use. Manufactured by: Bioniche Teo. Inverin, Co. Galway, Ireland

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Date of Preparation: July 2000.

Revised: March 2006.

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European Patent no: 0813417 – U.S. Patent no: 5.591.724.5.880.108.5.888.9 – Canadian Patent no: 2.203.62

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