URINARY TRACT INFECTIONS

AN UPDATE ON MODERN CLINICAL PRACTICE

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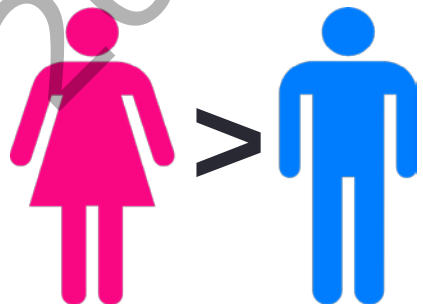
September 2019

INTRODUCTION

Urinary Tract Infections (UTIs) are the most common bacterial infectious disease worldwide



Affects disproportionally more women than men

Symptoms: Irritation, urgency, frequency, dysuria

National Institute of Clinical Excellence (NICE) defines UTIs as “the presence of bacteria in the urine with a combination of clinical features indicating an infection of the urinary tract.”

Huge financial cost

- Most common presentation to primary care in UK and USA
- 50% women experience in lifetime

Recurrent UTIs

- **Recurrent UTIs** = *"three or more episodes of UTI during a twelve month period or two or more within 6 months"*
- **Two types**:
  - Persistent (95%) – same organism
  - New – different organism
- Occurs in 20-30% women with previous UTI history
- Often requires **continuous** low dose **antibiotic prophylaxis**
- Rising **resistance** triggered **WHO Global Action Plan**

World Health Organization

Diagnosis

- Urine dipstick
  - **Blood**: Present in severe infection from lining inflammation
    - False positives from malignancy, stones, renal disease, dehydration
  - **Leucocytes**: white cells in urine, neutrophils produce leucocyte esterase which reacts with dipstick
    - Takes **2 minutes** for reaction to occur - therefore need to wait!
    - Sensitivity 50-70%
  - **Nitrites**: Gram negative bacteria converts urinary nitrates to nitrites
    - 92-100% specificity in literature to presence of infection
    - Sensitivity between 35-85% in literature – many bacteria unable to concert nitrates to nitrites
- **MC&S** – gold standard for diagnosis and sensitivities
  - $>10^5$/ml is deemed diagnostic for a UTI
  - Between 10^2 and 10^4 associated with infection – increased voiding from bladder irritation and increased hydration, washes out bacteria within bladder, produce falsely low level.
- **Asymptomatic positive MC&S** – present in up to 20% of menopausal women, usually from peri-urethral colonisation
  - Not for routine treatment
  - Treat only in presence of risk factors - pregnancy, immunosuppression, planned surgical instrumentation

Imaging

- Indicated in:
  - Failure to respond to treatment
  - Recurrent infections
  - Critically ill patient
  - Suspicion of functional/structural abnormalities

- USS KUB – first line
  - Detects hydronephrosis, parenchymal abnormalities, peri-nephritic collections, ureteral dilatation, bladder wall abnormalities, calculi (user dependent, smaller ones often missed)
  - Requires full bladder to visualise lining and assess bladder contents (if catheterised, clamp catheter)
  - Measures post void residual

Imaging

- CT – KUB – non contrast low resolution (often low dose) scan to detect stones
  - Can detect other intraabdominal issues (diverticulitis, AAA, appendicitis, masses, but poorer sensitivity)
  - Effective dose (measures risk to patient from the radiation of a scan) of low dose CTKUB is very low
    - similar or lower than XR KUBs in obese patients

- CT-Urogram – contrast study, with delayed phase to allow contrast opacification of ureter
  - Detects ureteric lesions/cause for hydronephrosis
  - Can also detect drainage and indirectly assess for PUJ-O

Imaging

- 99m Tc-DMSA – radionuclide imaging – used to detect scarring post pyelonephritis in kidneys and differential function between the two kidneys

- MRI – utilised for patients with contrast allergy or contraindication to radiation (e.g. pregnancy)
  - Very claustrophobic tube
  - Poor at detecting calculi
  - Especially good at detecting abscesses within prostate in prostatitis

Antibiotics

- Utilise according to local guidelines and previous sensitivities

Options to use in clinic

- **Trimethoprim** – resistance rates up to 70% in areas of UK
- **Nitrofurantoin** – warn of risk of lung fibrosis and hepatotoxicity from long term use, needs adequate renal function for use
- **Penicillin** – Also rising resistance rates (50% in areas of UK to amoxicillin)
- **Fluroquinolones** – especially good for prostatitis/epididymitis/orchitis. However warn patient of risk of tendon rupture with prolonged use
- **Cephalosporin** – similar MOA as penicillin, but less susceptibvel to B-Lactamases
- **Fosfomycin** – given as a STAT oral megadose

- ***Aminoglycosides*** *– Urologists favourite! Be aware of ototoxicity and nephrotoxicity with gentamicin use. Can be given IV or IM.*

Current antibiotic – free preventatives

Conservative, Cranberry, Hiprex, D-Mannose, Herbal, Oestrogen

Conservative

- **Increase fluid intake –** advise to drink 2 - 3 litres per day overall.
  - In patients who drink less than 1.5L per day, advise an additional 1.5 litres to their usual fluid intake per day

- **Sexual hygiene** – increased coital frequency, sexual partners, use of diaphragms and spermicide increase risk of UTI.
  - Advise pre coital genital washing, post coital micturition, wiping front to back.

- **Personal hygiene** – advise care when shaving or using products around the genital-urinary region, regular underwear changes and avoid tight fitting undergarments.

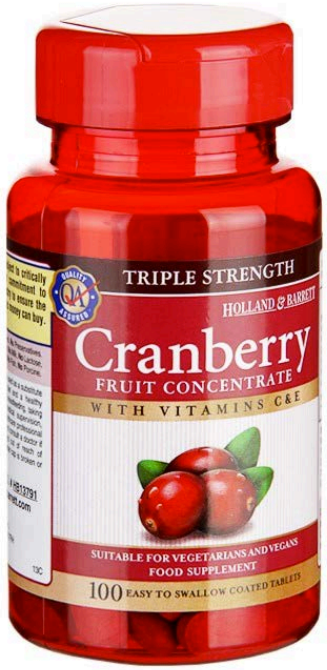
- **Voiding –** advise techniques to reduce amount of residual urine in bladder post void, including double voiding, pelvic floor exercises and pelvic tilting

- **Weight loss –** higher risk of UTI and pyelonephritis if BMI over 30

Cranberry

Cranberry (Vaccinium Macrocarpon) – juices, tablets, capsules

- Active ingredient = **Proanthocyanidins (PAC)** within cranberry bind to bacterial P-Fimbriae – inhibiting adherence to bladder epithelial cells



2012 Cochrane – 4473 participants

NO significant difference found vs placebo, water etc

However cohort included complex patients (eg spinal cord injury, elderly, children etc)

2008 Cochrane review - 10 trials overall found a relative risk reduction of 0.65 (95% CI 0.46 to 0.90)

Did NOT include "complex" patients

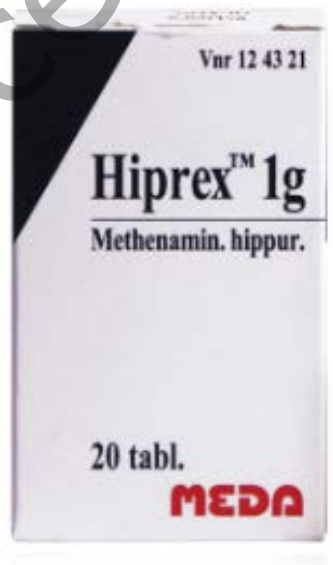
Note: *quality of data lacking due to no standardization in type of cranberry product used and dosage*

All trials had high dropout rates

Hiprex

Methenamine Hippurate (Hiprex)

- Renal excretion of methanamine salts undergoes hydrolysis and formation of formaldehyde – bactericidal
- Hippuric acid acidifies urine, promotes hydrolysis of methanamine and has bacterial static effect in itself



2012 Cochrane – 2023 participants

Relative risk reduction of 0.24 in patients **ONLY** if no underlying anatomical abnormalities within renal tract.

Potentially more effective with Ascorbic acid (vitamin C) – further acidifies urine

1g BD (TDS if presence of indwelling catheter)

D-Mannose

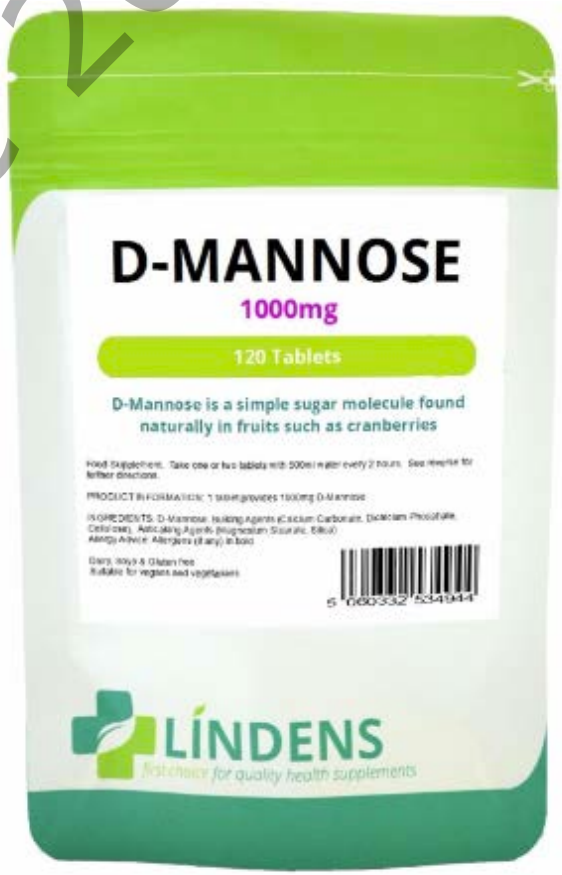
Originally used in cats, dogs and horses!!

- Natural sugar within human metabolism, inhibits adherence of bacteria to urothelial cells via inactivation of surface fimbriae

2014 RCT – 308 participants
2g dissolved in 200mls water daily significantly better vs nitrofurantoin prophylaxis and placebo

However still lacking more high quality placebo controlled RCTs

Note: *can be sold and given in combination with cranberry supplements!*



Herbal

- Traditional Chinese medicine – over 2000 year history of treating UTIs
  - Believes kidney is key to metabolism of water in body, and failure of kidney to remove “dampness” and “heat” from bladder causes symptoms of painful urination and UTIs.
  - Options include ***Er Xian Tang (二仙片), San Jin Pian (三金丸) Ba Zheng (八正)***

- Poor clinical evidence from Asia
  - No report on assessor blinding
  - No power calculations or if sufficient numbers were recruited to claim statistical significance
  - Significant loss of patients to follow up
  - Failures to standardise TCM preparations
  - Failure to mention side effects

- *Bazheng* powder (Ba Zheng San UTflow™, 八正) has one quality double-blinded trial in China in patients with recurrent UTIs.
  - 122 female patients received either *Bazheng* Powder for 4 weeks or antibiotics for 1 week, followed by 3 weeks of placebo.
  - Clinical cure rate, microbiological cure rate (negative urine culture) and recurrence after treatment were evaluated.
- Bazheng was found to be more effective than antibiotics in preventing UTI recurrence (9.1% recurrence rates with BaZheng vs antibiotics 14%)

Accupunture

- Fine needles inserted into pressure points
  - Helps **correct the flow of Qi** (life force within body) which is disrupted in disease

- 2 Norwegian studies on use of acupuncture at UTIs
  - Overall nearly 200 women
  - Compared to “sham” acupuncture group (!)
  - During the observation period (6-12 months), **half as many UTI episodes per person-month occurred in the acupuncture group** compared to the control group (RR = 0.45; 95% CI 0.23- 0.86).

  - Women in the acupuncture group experienced a **50% reduction in residual urine after 6 months** relative to baseline (35.4 vs 18.2 mL; P ≤ 0.01)
    - whereas women in the untreated group exhibited no significant change in residual urine (35.5 vs 38.8 mL).

Oestrogen

- Loss of protective acidic vaginal environment after menopause due to low oestrogen levels
  - Loss of commensal *lactobacillus* which proliferate with oestrogen
- Oestrogen replacement already in use in treating menopausal symptoms and atrophic vaginitis

- Vaginal oestrogen: Cochrane study involving 3345 women.
  - When comparing vaginal oestrogen and placebo, reported vaginal oestrogen was effective at preventing recurrent UTIs
  - Risk reduction of between 0.25 (95% CI 0.13 to 0.50) and 0.64 (95% CI 0.47 to 0.86)

- Example: Vagifem 1 tablet daily for 2 weeks, then 1 tablet twice a week – administered vaginally

- Oral oestrogens and vaginal high dose pessaries has shown higher levels of absorption systemically with more side effects
  - NOT RECOMMENDED BY NATIONAL/INTERNATIONAL GUDEINES FOR UTIS

New antibiotic – free Preventatives

Instillations, Immuno-modulators, Vaginal Lasers

Instillations

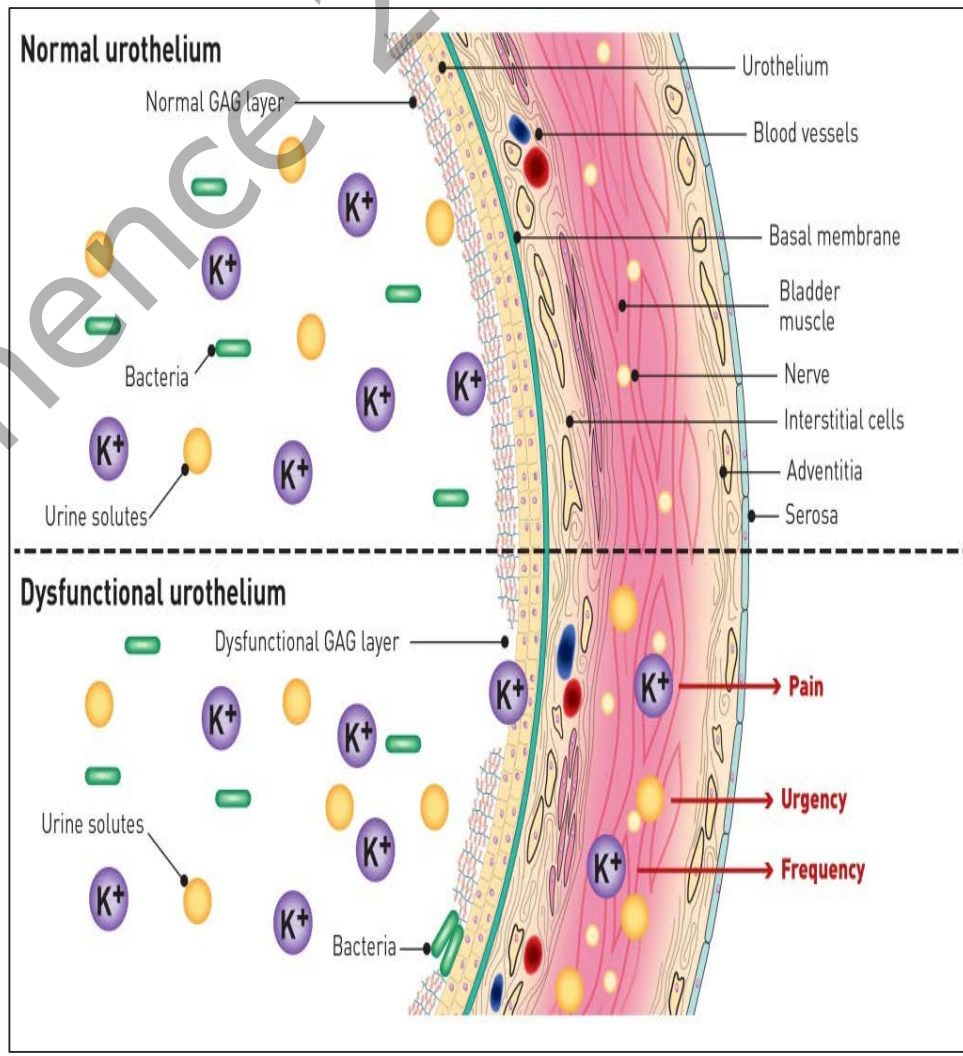
Intravesical instillation

Intact bladder epithelium and glycosaminoglycan (GAG) layer prevents bacterial adherence

Loss of this layer increases risk of rUTIs

Instillation of **Hyaluronic Acid** or **Chondroitin Sulphate** via catheter restores this layer

- Administered in outpatient clinic
- Negatives: Catheter related issues, invasive, requires clinic attendance



Intravesical options

- **Cystistat®** (Bioniche Life Sciences Inc., Belleville, Ontario, Canada)
  - Contains HA only

- **Ialuril®** (Aspire Pharma, UK) is another instillation option
  - Comprising of a mix of HA and CS.
  - More evidence for effectiveness, including a multicentre prospective trial and a placebo RCT

  - NOTE: Ialuril introduced in 2018 new catheter free administration device – similar to administering Instilagel.
    - Long term efficacy data on this device is not yet available

Ialuril® in Reading

- **First patients** in Reading June 2010
- Usually course of 6 treatments
  - One week apart for the first month then two weeks for a month then maintenance treatment monthly
  - Patients self treat when possible after supervised training.

- All patients recruited have had **>3 microbiologically proven UTIs in previous 6 months**
  - No correctable urological abnormalities
  - Life style optimized
  - Failed conservative treatments
  - Failed or unwilling to take low dose prophylactic antibiotics

Ialuril® in Reading - Results

100 patients

- Mean age: **48 years**
- Average number of UTI episodes in 12 months: **6.4**
- PUF score **22**

- **66** patients **infection free**, at end of treatment
- 27 patients **further infection** but many felt improved
-
- *7 patient discontinued after 2 treatments*

HA and CS – 2016 European Study

276 women – multi-centre across eurpe

- Compared against low dose antibiotic prophylaxis

- **Reduced UTI recurrence risk by 49% over 12 month**

- Increasing number of instillations associated with better odds ratio at preventing recurrence

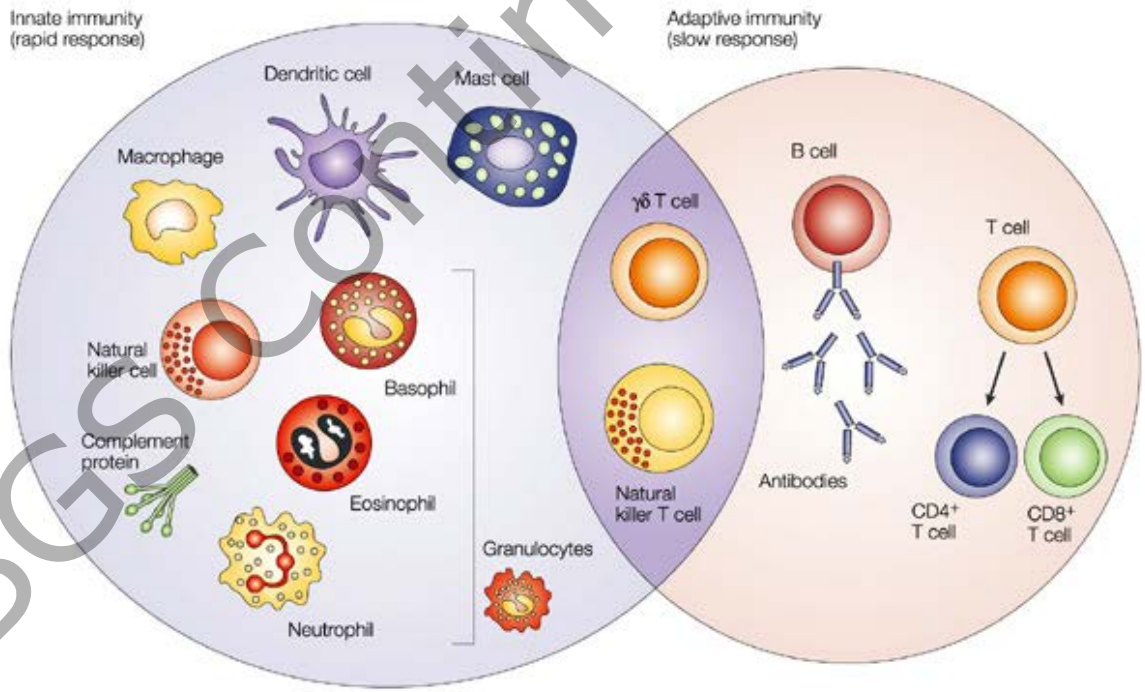
- *Only large study available to data which compared installation to antibiotic prophylaxis (current gold standard)*

Immuno-modulators

Vaccines - Immunomodulation

- Genitourinary tract harbours innate and adaptive mucosal immune system
  - Mucosa-Associated Lymphoid Tissue (MALT) as part of Mammalian lymphoid organ system

- **80% all immunocytes** in body contributed to by this system



THEORY

2 landmark papers:

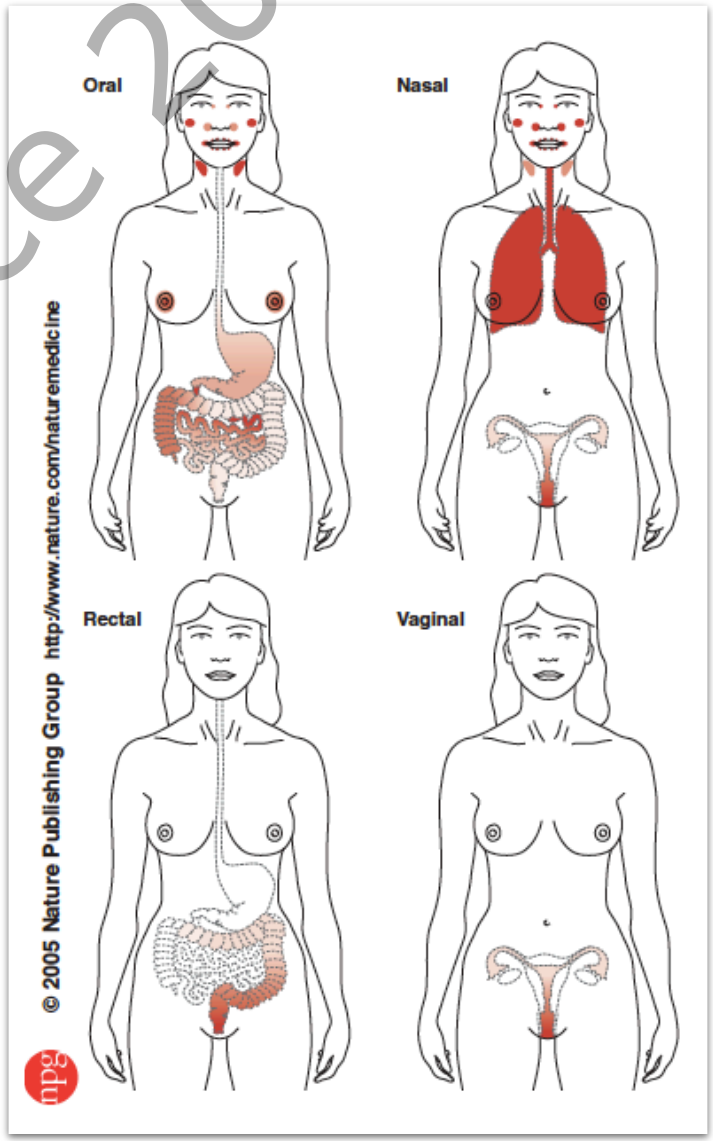
- ***Holmgren et al*** *(Nature 2005) and* ***Villalvilla et al*** *(Immunology 2016):*

- Various Mucosal stimulation induces immunocyte response locally and at distant mucosal site

- Diagram showing expression of mucosal IgA immune response after various routes of vaccination
  - Shading indicates strength of response

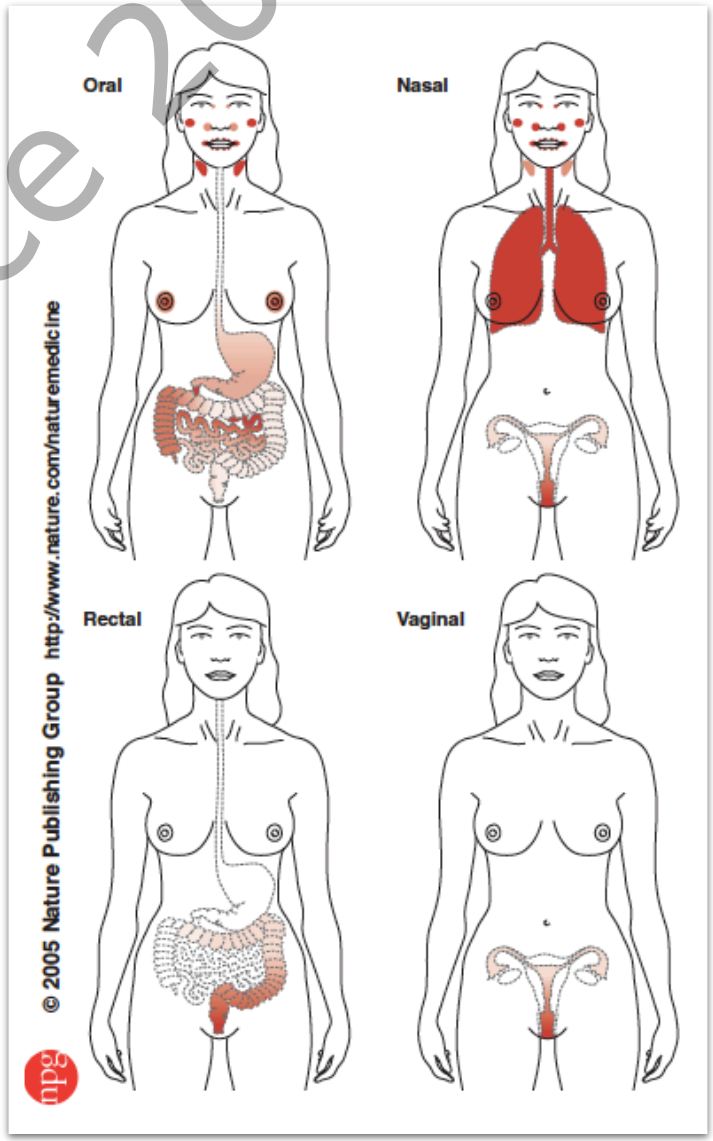
- In humans: Cholera toxin B stimulation induces strongest responses in:
  - Vaccine exposed mucosa
  - Adjacent or interconnected mucosa.

- In **nasal/oraphrangeal mucosa** – strong stimulation also in **genital vaginal mucosa.**



THEORY

- For immunomodulation vaccines:
  - Sublingual **linked** with genitourinary system:
- Sublingual stimulant induces both Toll-Like-Receptors on Dendritic Cells and activates T Cells
- **Broad spectrum immune response** via recognition of lipopolysaccharide on outer membrane of uropathogen



Vaccine options

- **Uro-Vaxom®** (Terralab, Croatia)
  - One of the first immuno-modulating vaccines
  - Bacterial extracts from **8 uropathogenic Escherichia Coli** strains
  -
- Tablet form – daily administration for 3 months

- Mixed results
  - 4 placebo studies with 3-12 months follow up showed relative risk of UTI development almost **halved** - 0.61(95% CI 0.48-0.78)
  - Recent large (451 patients) double blind control trial showed **no significant difference vs placebo**

Another vaccine option

- **Uromune®** (Syner-Med (PP) Ltd UK, Inmunotek S.L. Spain)
  - Pre-license Phase III development stage
  - Inactivated whole bacteria - *Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris and Enterococcus Faecalis*
  - 3 month course of sublingual spray twice a day
  - Currently manufactured and used in Spain
  - No double blind RCT results currently however:
  - **Two large studies** showing effectiveness vs antibiotic therapy
  - One **UK prospective study** showing effectiveness

Int Urogynecol J (2013) 24:127–134
DOI 10.1007/s00192-012-1853-5

ORIGINAL ARTICLE

Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics

M. F. Lorenzo-Gómez · B. Padilla-Fernández · F. J. García-Criado · J. A. Mirón-Canelo · A. Gil-Vicente · A. Nieto-Huertos · J. M. Silva-Abuín

Received: 11 April 2012 / Accepted: 3 June 2012 / Published online: 18 July 2012

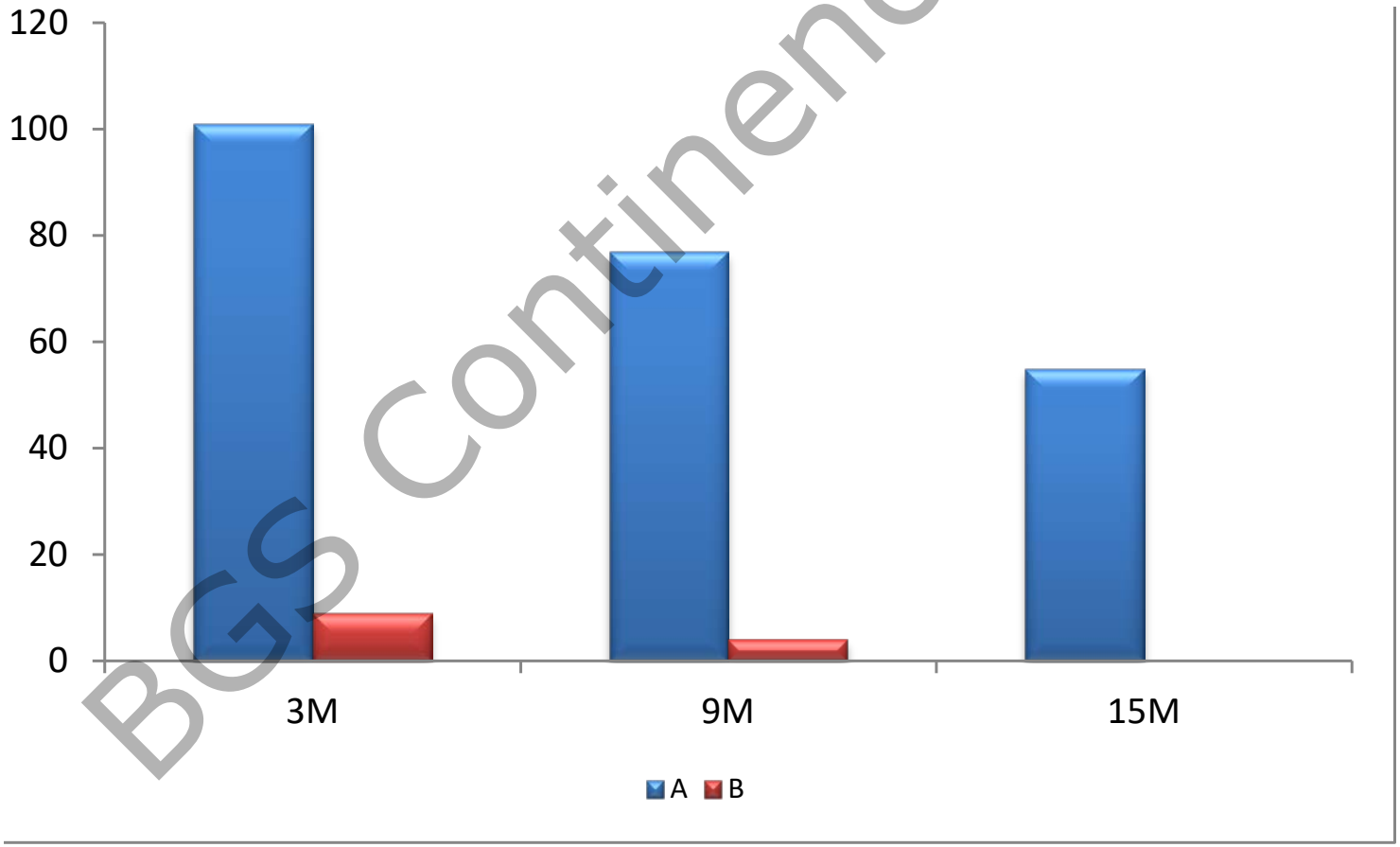
First Spanish Study

Observational Retrospective Study

- 319 patients in total
- Uromune: **159 patients**
- Co-Trimoxazole antibiotic prophylaxis (Trimethoprim/sulfamethoxazole): **160 patients**

Results

- Patient's free of UTI at follow up
  - (A = Uromune, B = Abx prophylaxis)
  - No side effects reported



frontiers in Cellular and Infection Microbiology

ORIGINAL RESEARCH
published: 03 June 2015
doi: 10.3389/fcimb.2015.00050

Comparison of sublingual therapeutic vaccine with antibiotics for the prophylaxis of recurrent urinary tract infections

María F. Lorenzo-Gómez[1,2,3]*, *Bárbara Padilla-Fernández*[4], *María B. García-Cenador*[3], *Álvaro J. Virseda-Rodríguez*[2,3], *Isidoro Martín-García*[5], *Alfonso Sánchez-Escudero*[6], *Manuel J. Vicente-Arroyo*[7] and *José A. Mirón-Canelo*[8]

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Objective: To compare the clinical impact of a prophylactic treatment with sublingual immunostimulation in the prevention of recurrent urinary tract infections (rUTIs) with the use of antibiotics.

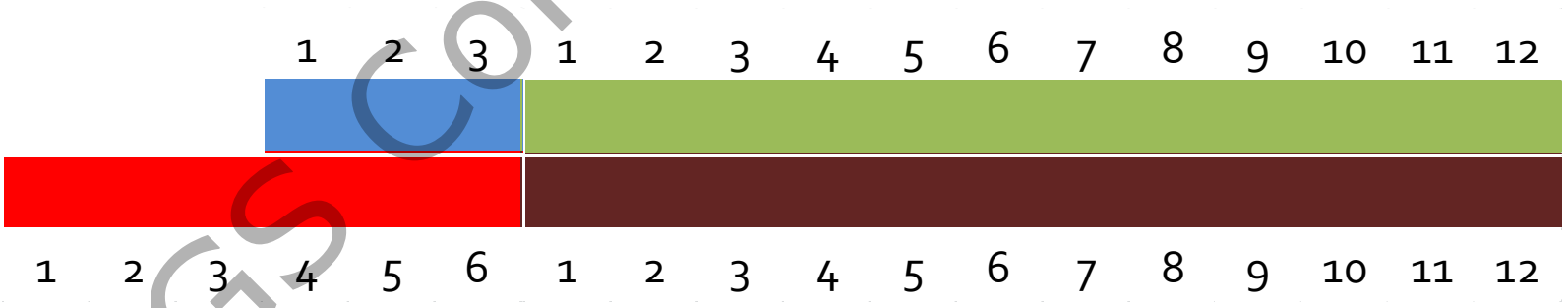
Material and Methods: Retrospective cohort study evaluating the medical records of 669 women with rUTIs; 339 had a 6-month prophylaxis with antibiotics and 360 a

Second Spanish Study

Larger Observational Retrospective Study

- 669 patients in total
- Comparing 3 months Uromune vs 6 months antibiotic (co-trimoxazole or nitrofurantoin) prophylaxis

Uromune (n = 360)



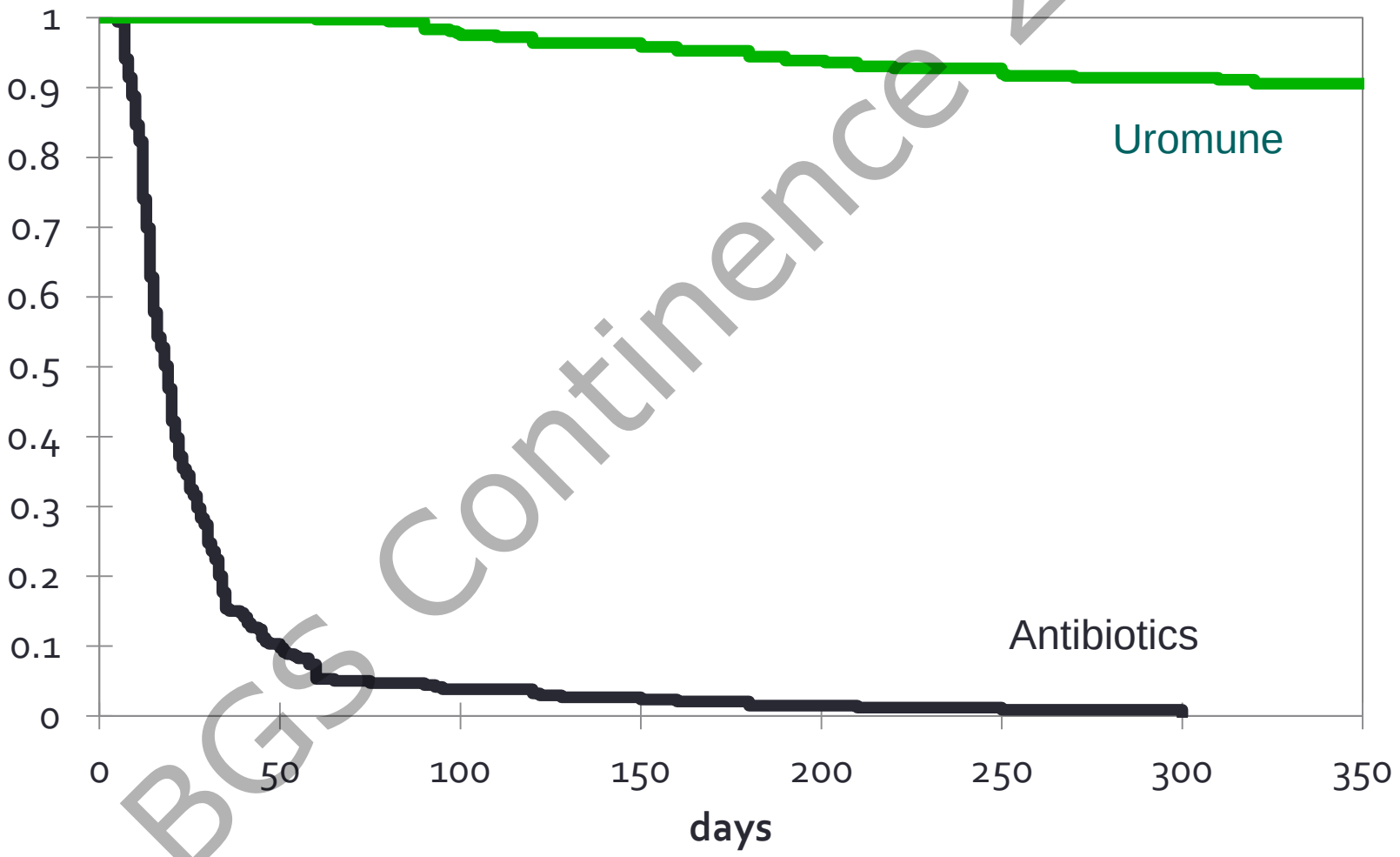
Antibiotic (n = 339)

Results

Uromune (n = 360) – **9.7% had new infection**

Antibiotic (n = 339) – **100% had new infection**

Results



BJUI
BJU International

Original Article

First experience in the UK of treating women with recurrent urinary tract infections with the bacterial vaccine Uromune®

Bob Yang, Stephen Foley

First published: 23 November 2017 | https://doi.org/10.1111/bju.14067 | Cited by: 1

Abstract

Objectives

To determine the effectiveness of Uromune® in preventing recurrent urinary tract infections (UTIs) in women.

Uromune in Reading

Prospective observational study at **Reading Urology Partnership**

Women with recurrent UTIs having **failed** conventional treatment

September 2014 – Today (ongoing)

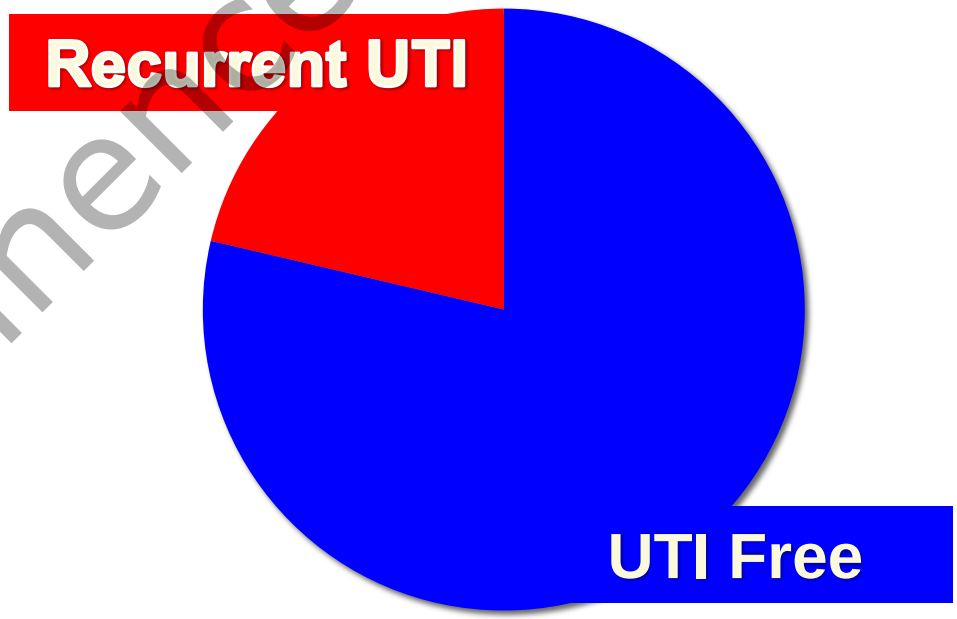
Also starting to use in men with prostatitis

RESULTS

75 out of 77 (97%)
completed treatment

- ***One patient*** *dropped out due to lifestyle and personal reasons.*
- ***One stopped*** *due to allergic reaction*

59 out of 75 (78%)
reported no subsequent UTIs



- **Pre-menopausal women**: 88% success rate
- **Post-menopausal women**: 72% success rate

Vaginal Laser Therapy

Laser Therapy

- **Thermo-ablative fractional CO2 laser**
  - Applied directly to vaginal mucosa
  - Repair and restores vaginal mucosa at cellular level
  - Similar pathway to oestrogen replacement therapy

- Significantly decreases symptoms of vulvo-vaginal atrophy and dyspareunia

- Early evidence of use in recurrent UTIs in post meno-pausal women

Laser Therapy

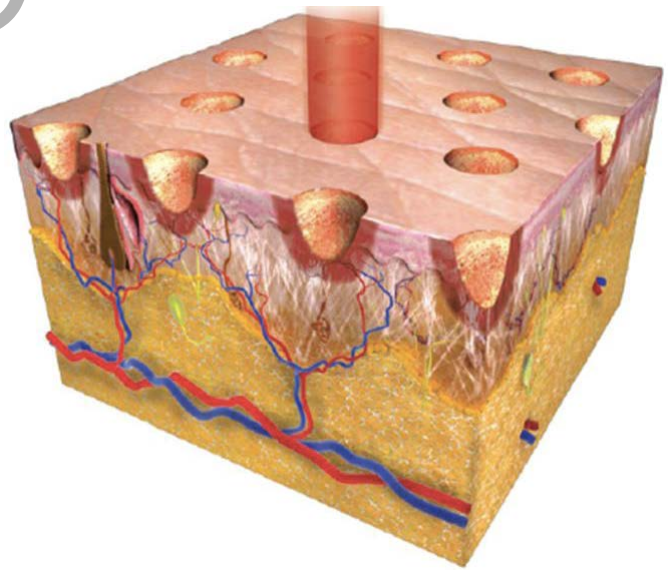
Controlled small ablation zones are created in the **lamina propria** using each offered energy level starting from 7.5 to 12.5mJ.

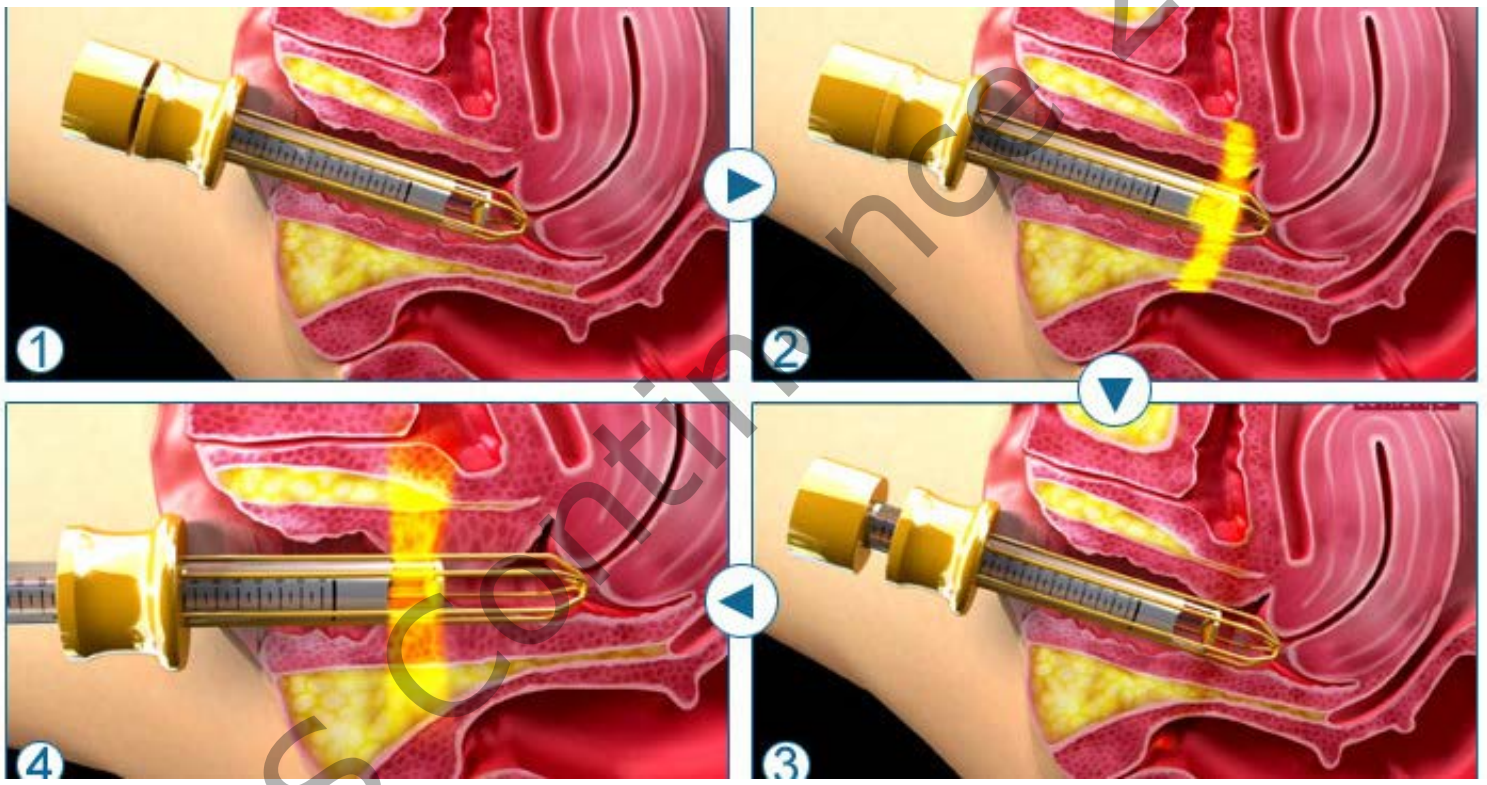
- Using these parameters allow to provide effective vaginal remodelling process while limiting penetration depth to up to 600µm
- Ensures safety of the fibromuscular layer
-

- Immediate collagen fiber contraction

- Initiation of new collagen and elastin synthesis

- Regeneration of the vaginal mucosa (1)
  - Epithelium becomes thicker
  - Beneficial effects are seen in the layers of the vagina (2)
    - Increased storage of glycogen in the large epithelial cells

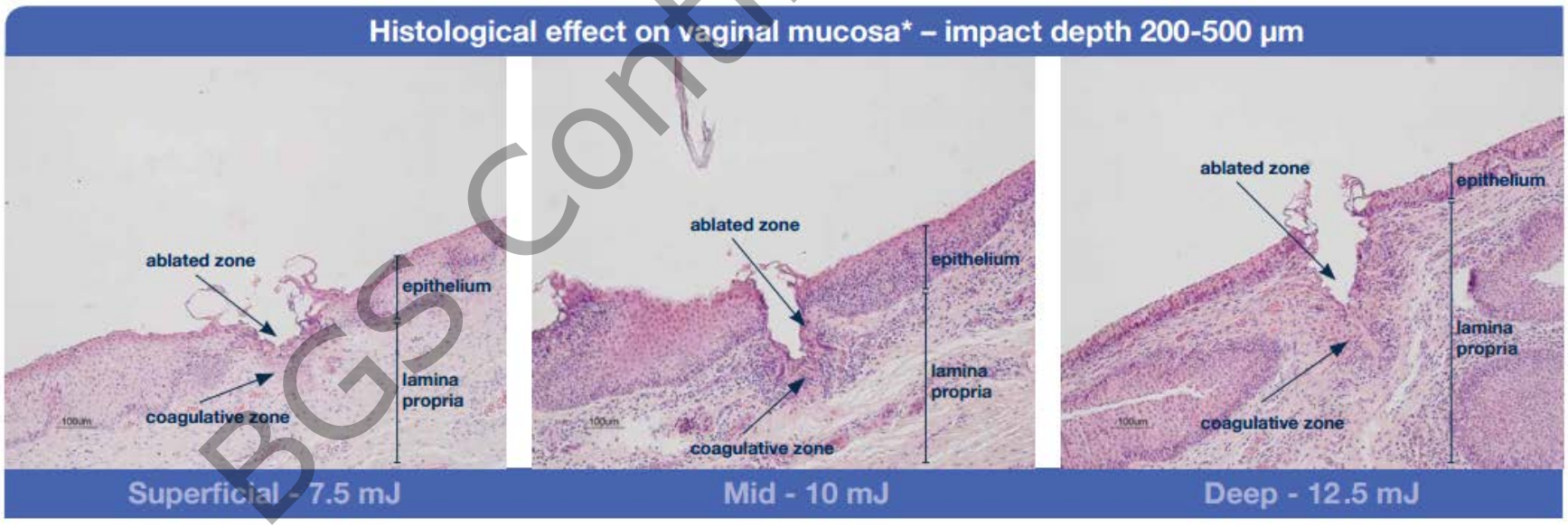




FemTouch™ - Controlled ablation & coagulation

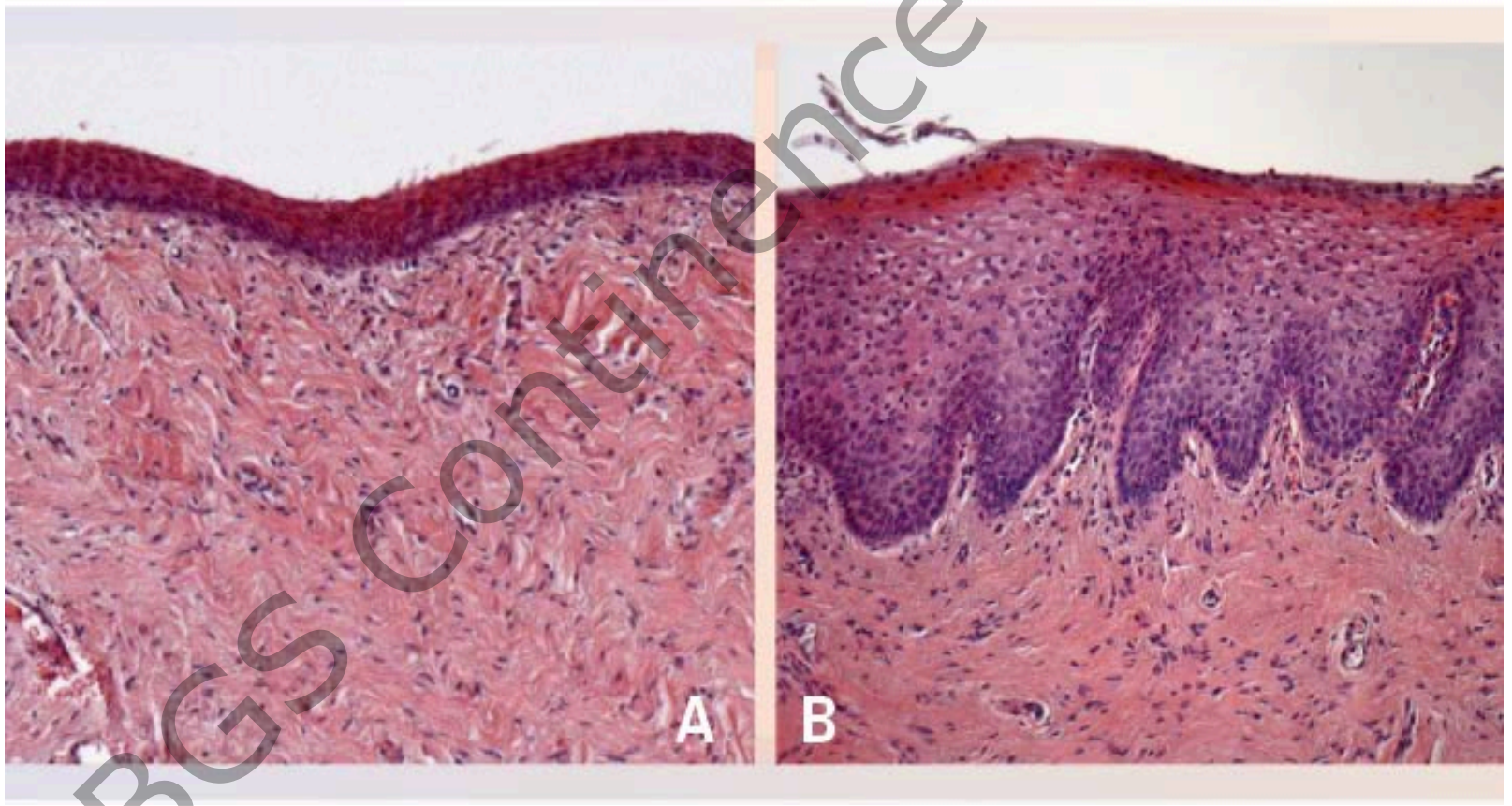
- The depth of penetration is controlled by the energy settings
- 210 micron spot size
- Uniform coverage
- Controlled gentle heating

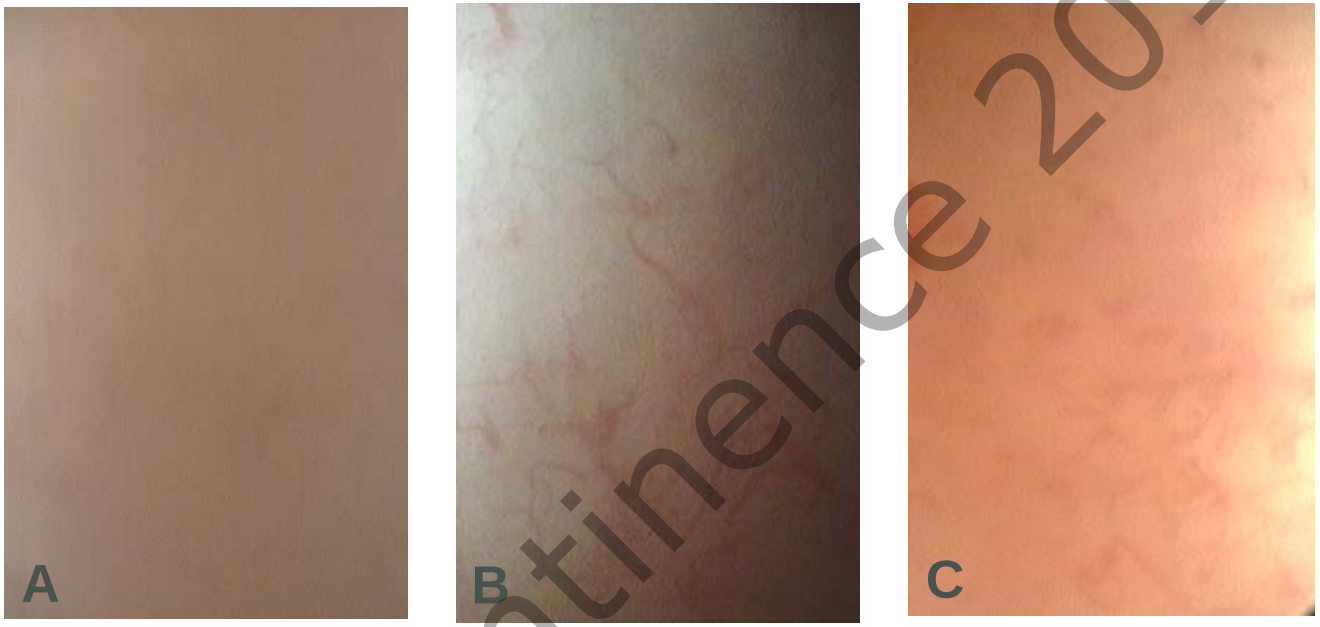
Minimal downtime



*porcine ex-vivo model

Laser therapy





A - Menopause, before treatment
B - Immediately following treatment
C - 3 months post treatment

FemTouch™ in Reading

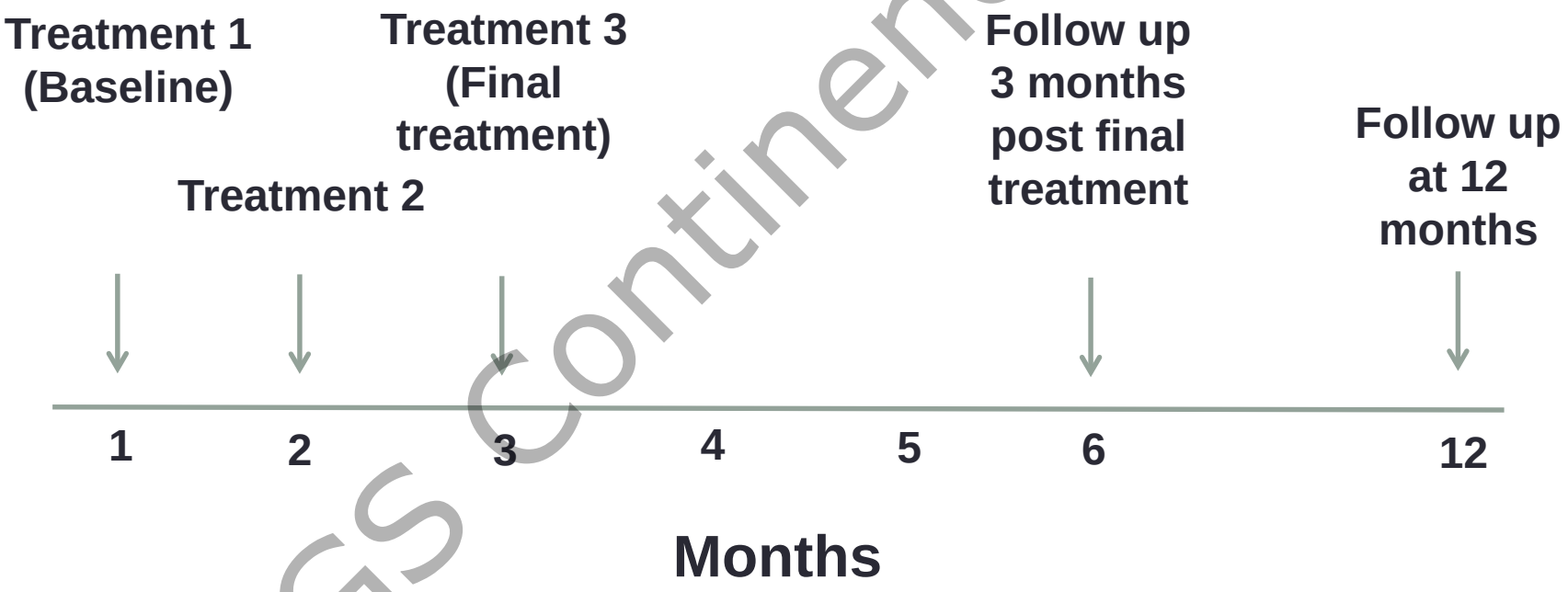
Registered audit at Reading Urology Partnership

12 women post menopause with **recurrent UTIs** despite conventional treatment

Preceding any intervention **all women** received a smear test for histological analysis as well as a vaginal swab for microbiology analysis

- This is to exclude any underlying **active infection** or **malignancy**, which would affect the suitability of the patient to undergo fractional laser therapy.

Study Design



Outcomes

All **12 patients** completed treatment

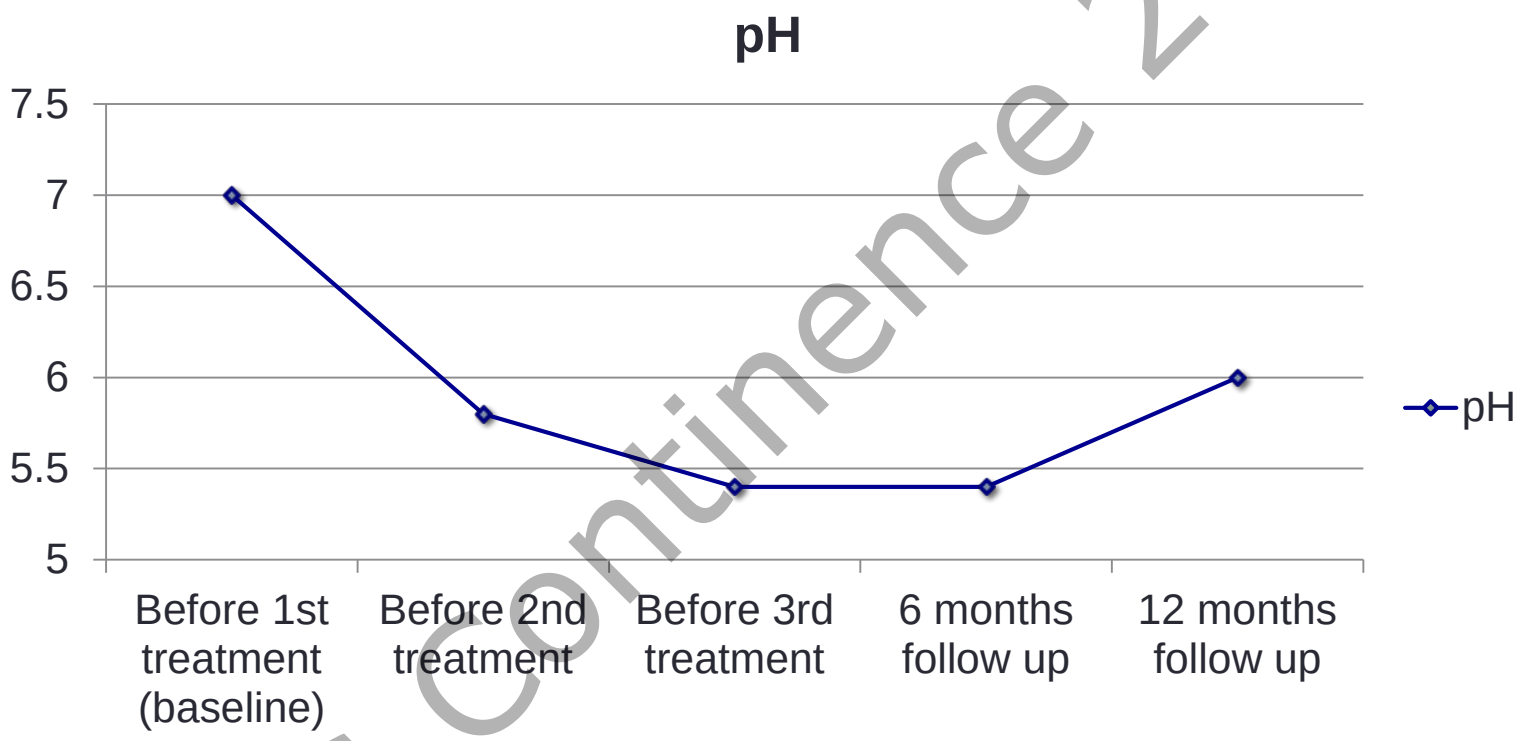
- **Visual analogue score** post treatment: rate treatment discomfort/ pain based on a visual analogue scale where the extreme left indicates "no pain" and extreme right indicates "intolerable pain"
- Score translated into scale of 1 – 10

All described treatment "pain" as **1 out of 10 on average** throughout

Of the 12 women, **11 women (92%)** remained UTI free by 6 months

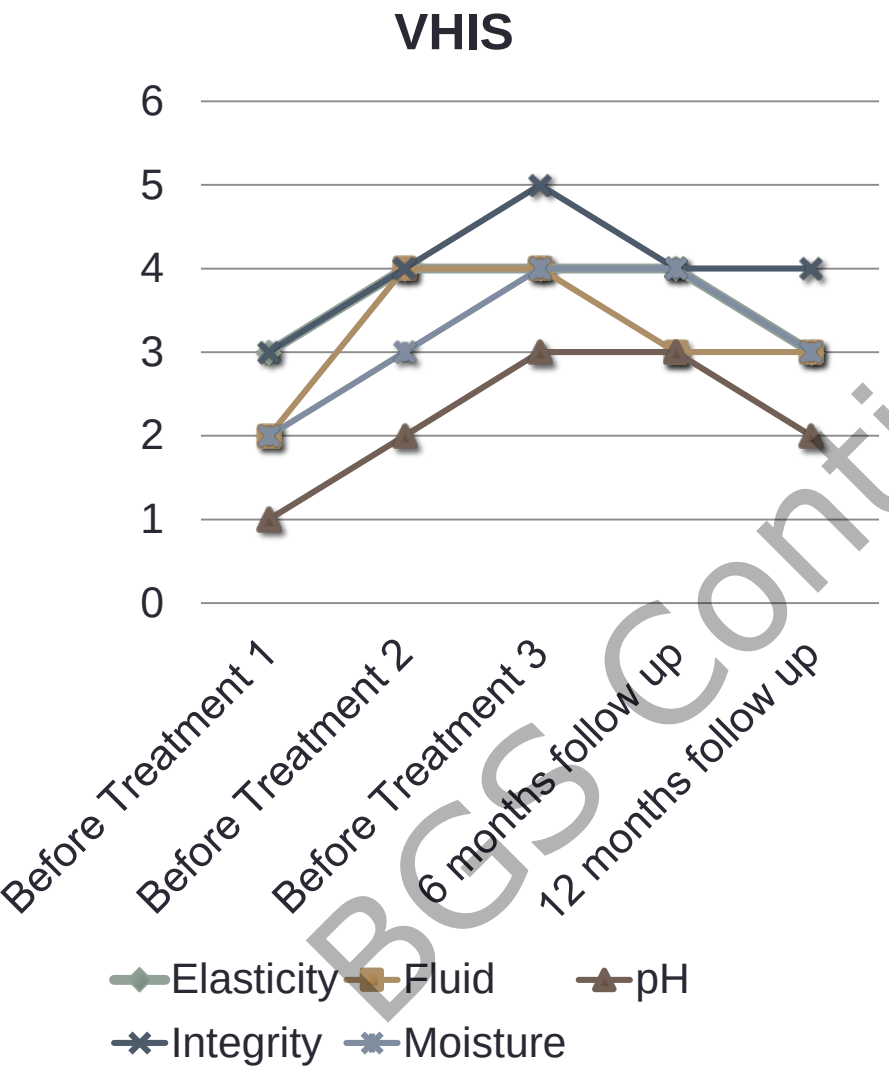
- **9 (75%) women** remained UTI free throughout the treatment and follow-up period.

Restoration of Acidity



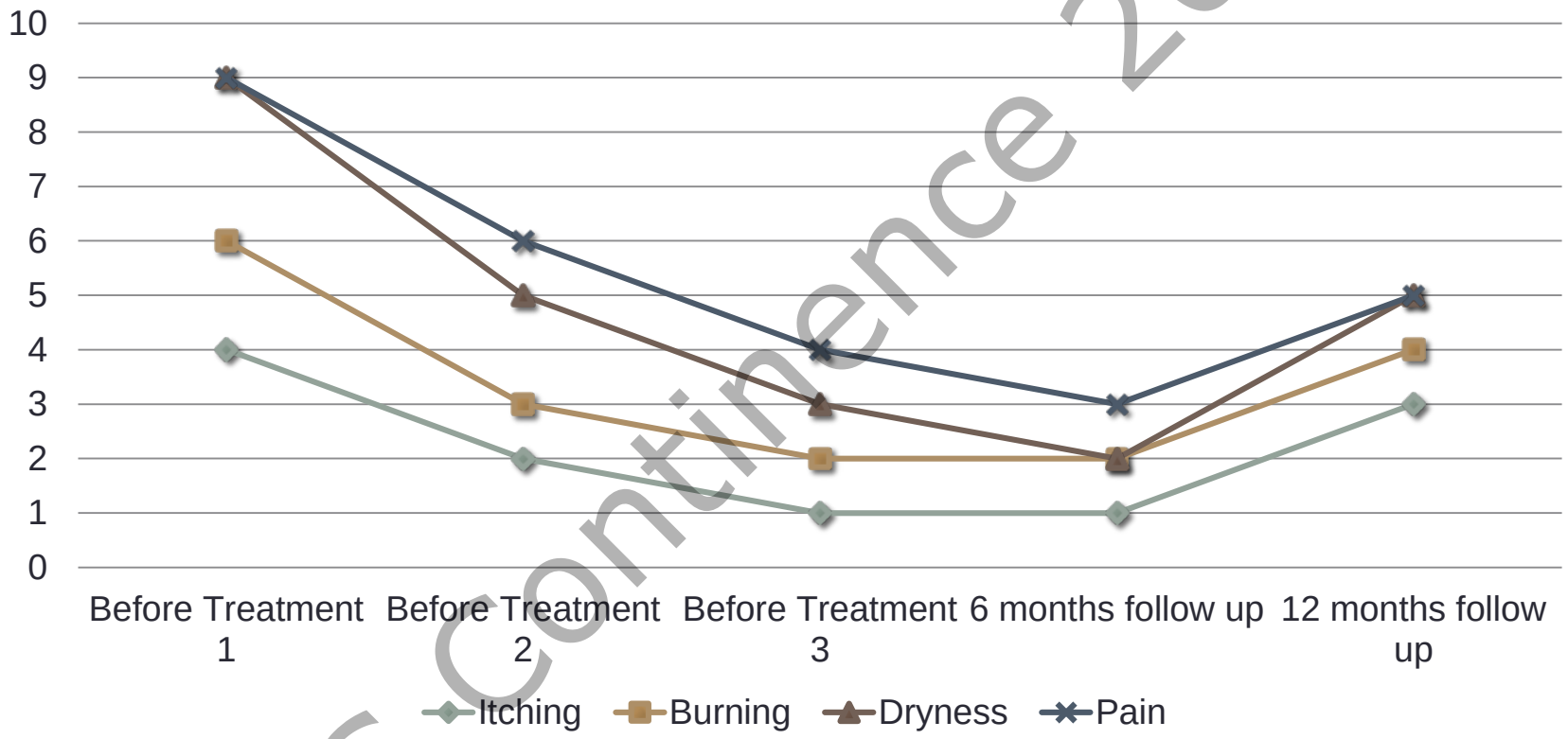
	Before 1st treatment (baseline)	Before 2nd treatment	Before 3rd treatment	6 months follow up	12 months follow up
pH	7.0	5.8	5.4	5.4	6.0

Restoration of Vaginal Health (VHIS)



Average VHIS (1 = poor, 5 = excellent)					
	Before Treatment 1	Before Treatment 2	Before Treatment 3	6 months follow up	12 months follow up
Elasticity	3	4	4	4	3
Fluid	2	3	4	4	3
pH	1	2	3	3	2
Integrity	3	4	5	4	4
Moisture	2	3	4	4	3
TOTAL	**11**	**16**	**20**	**19**	**15**

Improvement of Vulvo-Vaginal Atrophy



	Before 1st treatment (baseline)	Before 2nd treatment	Before 3rd treatment	6 months follow up	12months follow up
Itching	4	2	1	1	3
Burning	6	3	2	2	4
Dryness	9	5	3	2	5
Pain	9	6	4	3	5
Total	**28**	**16**	**10**	**8**	**17**

Conclusion

Very early days

- Benefit especially in previously difficult patient groups, in particular previous **breast cancer history** and cannot tolerate oestrogen
  - Cheap
  - Easily administered
  - Virtually painless
  - Promising results
  - Restores sex life!

Aiming to determine effects in **larger groups** of patients for **longer follow up** period

- Enough merit to set up large **multi-centre study**

Lots of potential

Any Questions?