Boffin Access
FOSTERING KNOWLEDGE

Open Access Journal | Volume: 1.1

Journal of Urinary Tract Infections

Outpatient electrofulguration for antibiotic-recalcitrant recurrent urinary tract infections in women with trigonitis alone.

JA Stevens[1]

JA Chavez[1]

AL Christie MS[2]

PE Zimmern M.D[1]

[1]Department of Urology, U.T. Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, Texas 75309-9110

[2]Simmons Comprehensive Cancer Center, U.T. Southwestern Medical Center, v 6000 Harry Hines Blvd.,
Dallas, Texas 75390-8852

Abstract

Objective

To evaluate the role of electrofulguration (EF) of trigonitis alone in women with antibiotic-recalcitrant recurrent urinary tract infections (RUTIs).

Methods

Following IRB approval, a retrospective chart review of women who underwent EF of inflammatory lesions limited to the trigone (trigonitis) to treat their antibiotic-recalcitrant RUTIs and had a minimum 1-year follow-up was undertaken. Primary (the primary) outcome was (the) number of symptomatic UTI episodes requiring antibiotics post-EF, leading to definitions of cure (0 UTI/year), improvement (1-2 UTI/year), and failure (≥3 UTI/year). (The secondary) Secondary outcome was (an) endoscopic success (group 1) or failure (group 2) based on complete trigonitis resolution during office cystoscopy 6 months post-EF.

Results

From 2008-2018, 40 women met study criteria (Group 1: 34 (85%) endoscopic success, Group 2: 6 (15%) endoscopic failure). There was no statistically significant difference in patient characteristics or pre-operative UTI management in the two groups. Median follow-up in group 1 was 3.7 years (IQR 2-6.1) and 2.3 years (IQR 1.7-7.5) in group 2 (p=0.71). Median urinary tract infections/year post-EF were 0.6 in group 1 and 0.9 in group 2 (p=0.89). Clinical outcomes between groups were not statistically different, with overall 9 (23%) cured, 29 (73%) improved, and 2 (5%) failed. In the clinically improved group, 19 (66%) had <1 UTI/year in the follow-up period starting 6 months post-EF. No patients remained on long-term, continuous antibiotic suppressive therapy after the follow-up 6 months cystoscopy.

Conclusion

EF resulted in endoscopic resolution of trigonitis in 85% of women with antibiotic-recalcitrant RUTIs, with durable clinical cure or improvement of RUTI in most patients.

Keywords

Trigonitis, Recurrent urinary tract infections, UTI, Electrofulguration

Introduction

Urinary tract infections (UTI) are extremely common with nearly 50% of women experiencing at least one episode in their lifetime [1]. As many as 100 of every 100,000 women in a national sample [2] will suffer from recurrent UTIs (RUTI), traditionally defined as 3 or more symptomatic UTI episodes in a single year [3-5]. RUTIs not only create a social and economic burden but also decrease the quality of life of afflicted women, leading to increased sick days, frequent office visits, multiple antibiotic prescriptions, and sometimes, rapid recurrence of UTI symptoms despite urine culture-targeted treatments [6]. Recent AUA Guidelines for managing uncomplicated RUTIs included the use of vaginal or systemic estrogen, low dose post-coital or self-start antibiotics, and continuous antibiotic prophylaxis [7, 8]. However, antibiotic-resistant

Article Information

DOI:	10.31021/JUTI.20211101
Article Type:	Research
Journal Type:	Open Access
Volume:	1 **Issue:** 1
Manuscript ID:	JUTI-1-101
Publisher:	Boffin Access Limited
Received Date:	26 January 2021
Accepted Date:	10 April 2021
Published Date:	21 April 2021

*Corresponding author:

Philippe E. Zimmern, M.D.

U.T. Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75390-9110
Telephone: 214.648.9397
Fax: 214.648.8786
Email:
Philippe.Zimmern@UTSouthwestern.edu

Citation: JA Stevens, JA Chavez, AL Christie MS, PE Zimmern M.D. Outpatient electrofulguration for antibiotic-recalcitrant recurrent urinary tract infections in women with trigonitis alone. J Urin Trac Infec. 2021 Mar;1(1);101

Copyright: © 2021 JA Stevens, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 international License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

bacteria and allergies have become an increasingly severe problem, limiting treatment options for women who frequently need antibiotic therapies [9, 10]. Non-antibiotic alternatives have gained renewed interest, including various formulations of Chinese herbs, methenamine hippurate, D-mannose, cranberry products, or lactobacillus containing probiotics [11]. Vaccination efforts are also under way [12], as well as [an(should remove)] increasing (the) use of intravesical agents such as Gentamicin [13].

The mechanisms by which these UTI recurrences occur have been debated in animal models [14, 15] and in(remove) humans [14]. Noteworthy has been the cystoscopic, office-based recognition of areas of chronic inflammation in the trigone (trigonitis) in many women with uncomplicated RUTIs [16]. In one study in which the trigone area of post-menopausal women with RUTIs was biopsied under anesthesia, direct evidence of bacterial presence by fluorescence in situ hybridization was observed, suggesting these sites of chronic inflammation correspond to bacterial persistence [17]. Such deep-seated niduses of infections are beyond the reach of antibiotics which can correct an acute infection but are unable to eradicate these bacteria which reside in protective biofilms [18].

One option to disrupt and remove these chronic trigonal lesions is to eliminate them with endoscopic electrofulguration (EF), a technique used for other bladder pathologies [19]. In a study of EF in the management of RUTIs in women with a variety of cystitis lesions involving the trigone and beyond, our group reported 75% resolution of inflammatory lesions and over 80% improvement in UTI rates [20]. Given the deleterious impact of RUTIs, the favorable outlook of EF, and the increased scrutiny on antibiotic efficacy to cure this condition, our goal was to study an optimal group of women with isolated trigonitis lesions and a history of uncomplicated RUTIs to determine if an outpatient EF procedure might curb years of repeated antibiotic exposure and possibly bring durable relief or decrease the rate of yearly UTIs. Since these women have a lesser burden of disease than those with more advanced cystitis, they could potentially respond better to EF. Therefore, using a long-standing IRB-approved RUTI repository database at our institution, we studied the endoscopic and clinical outcomes of women treated by EF for antibiotic-recalcitrant uncomplicated RUTIs with documented trigonitis alone.

Methods

Following IRB approval, the charts of non-neurogenic women who underwent EF of inflammatory lesions confined to the trigone (trigonitis) for uncomplicated RUTIs, had a 6 months post-EF office cystoscopy, and then were followed for a minimum of 12 months were reviewed. Excluded were women with a complicated history of RUTIs (urinary catheters, suprapubic tube, intermittent catheterization), another surgical procedure (cystocele repair, mesh removal, bulking agent injection, urethral dilation) at the time of EF, inflammatory lesions extending beyond the trigone, insufficient follow-up, and a recognized source for their RUTI after thorough office evaluation. A preliminary analysis stratifying patients based on previous urologic surgery showed no statistically significant differences in patient characteristics or outcomes from those with and without prior urologic surgery, allowing these patients to be combined in the final analysis (data not shown).

The definition of RUTIs came from a review of the literature, where the most accepted definition was ≥3 symptomatic UTI episodes/year with positive urine cultures [3-5]. Given the nature of our tertiary care center, all patients were extensively evaluated for etiologies of their UTI recurrences, including upper tract studies [21], pelvic examination, assessment of post-void residual

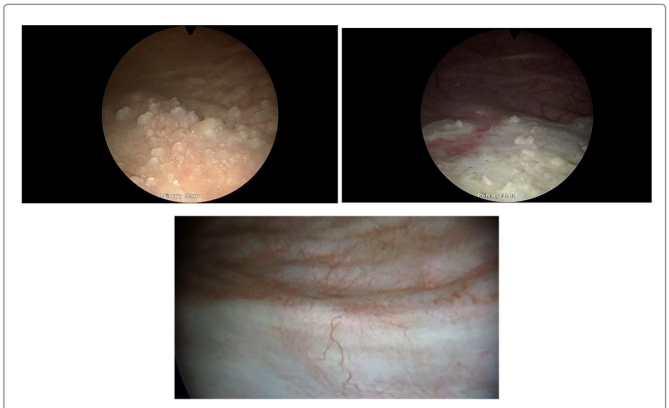

Figure 1: Top left: trigonitis with cystitis cystica. Top right: trigone after fulguration. Bottom: healed trigone at 6 month cystoscopy.

by bladder scan (< 50 ml), and a standing voiding cystogram [22]. An office cystoscopy was performed by an FPMRS trained faculty or physician assistant, under local anesthesia, and with a flexible cystoscope. Prior antibiotic courses and bacterial strains were obtained from outside reports, and subsequent cultures and antibiotic courses were recorded from an electronic medical record for those who pursued coital prophylaxis, self-therapy, or daily antibiotic suppression as per current guidelines.

Women who elected EF had (a) negative urological evaluation for other sources of UTI except (for) trigonitis and a sustained or repeated need for chronic suppression and/or acute courses of antibiotics to control their UTI symptomatology. Their RUTIs were classified as antibiotic-recalcitrant secondary to high rates of antibiotic-resistance (≥3 antibiotic classes), antibiotic allergies (≥3 documented allergic reactions), and/or no durable response to long-term antibiotic suppression (3-6 months or more).

EF was performed under anesthesia on an outpatient basis by an FPMRS faculty. Lesions of trigonitis including cystitis cystica, pus pockets, small, encrusted areas, and reactive inflammatory bladder neck polyps were documented by intra-operative photographs (Figure 1). A 17.5-Fr urethra cystoscope with a fine tip monopolar Bugbee electrocautery on a setting of 20 was used to superficially fulgurate the inflammatory lesions seen over the trigone. Most patients were discharged home after a voiding (maybe avoiding) trial while some elected to keep a catheter overnight due to distance from home.

The burning effect of the fulguration provokes a phase of initial scar formation on the bladder surface followed by a gradual elimination of this superficial scar in a wet urinary milieu, taking approximately 6 months to reach complete healing. Our secondary outcome was based on cystoscopy at 6 months after EF to ensure complete trigonal healing and no new areas of inflammation. EF was considered endoscopically successful if there were no inflammatory lesions remaining (no inflammatory lesions were) and the trigone had fully healed. Those with endoscopic success were placed in group 1 and those with failure in group 2.

The primary outcome was the number of UTI episodes/year starting after cystoscopy 6 months following EF, documented either by positive urine culture and/or an antibiotic course for UTI-like symptoms. During the follow-up period, patients were classified as clinically cured if they had 0 UTIs per year, improved if less than 3 UTIs per year and failure if 3 or more UTIs per year. Since most patients fell in the category of clinically improved, that subgroup was further divided into 0-1, 1-2, or 2-3 UTIs per year.

Post-EF follow-up including office visits, telephone encounters, and MyChart messages were (was) reviewed to record

	Success (n = 34)	Failure (n =6)	*P*
Median years of follow-up(IQR)	3.7 (2-6.1)	2.3 (1.7-7.5)	0.71
Median age, years (IQR)	56 (50-62)	73 (46-83)	0.11
Race			
White	32 (94%)	5 (83%)	0.39
Hispanic	1 (3%)	1 (17%)	
Other	1 (3%)	0(0%)	
Median BMI (IQR)	28.3 (23.1-32.9)	27.8 (27.2-31)	0.57
Median Party	2 (1-3)	2 (1-2)	0.81
Diabetic	5 (15%)	0 (0%)	>0.99
Ever Smoker	15 (44%)	1 (17%)	0.37
Prior urologic Surgery	22 (65%)	4 (67%)	>0.99
Hysterectomy	11 (32%)	2 (33%)	>0.99
Menopause/oophorectomy	26 (76%)	5 (83%)	>0.99
HRT	20 (59%)	3 (50%)	>0.99
Sexually active	19 (58%)	3 (50%)	>0.99
Past Suppressive antibiotics	15 (44%)	2 (33%)	>0.99
Past post – coital prophylaxis	3 (9%)	1 (17%)	0.49
Past IV anitibiotics	1 (3%)	0 (0%)	>0.99
Past pyelonephritis	6 (18%)	1 (17%)	>0.99
Median length of surgery, min (IQR)	5 (15%)	1 (17%)	>0.99
Post – fulguration outcomes			
Repeat fulguration	1 (3%)	1 (17%)	0.28
Median UTIs/year (IQR)	0.6 (0.2-1.1)	0.9 (0.3-1.6)	0.89
Clinical Outcome			
Success	8 (24%)	1 (17%)	0.28
Improvement	24 (71%)	5 (83%)	
Failure	2 (6%)	0 (0%)	
Post – fulguration Cultures			
E. coli	15 (44%)	3 (50%)	>0.99
Multiple Organisms	12 (35%)	1 (17%)	0.64
Drug resistant	5 (15%)	0 (0%)	>0.99
FQ - resistant	3 (9%)	0 (0%)	>0.99
Bactrim - resistant	5 (15%)	1 (17%)	>0.99
ESBL	2 (6%)	0 (0%)	>0.99
Post – fulguration			
Post – coital prophylaxis	8 (24%)	1 (17%)	>0.99
Self – start antibiotics	6 (18%)	1 (17%)	>0.99
IV antibiotics	2 (6%)	1 (17%)	0.39
Pyelonephritis	1 (3%)	1 (17%)	0.28

Table 1: Patient Characteristics by type of endoscopic outcome.
Abbrevations: *IQR = Interquatile range, BMI = body mass index, IV = intravenous, UTI = urinary tract infections, ESBL = extended – spectrum beta –lactamase, FQ = fluroquinolone*

all UTI-like symptoms, urine cultures or antibiotic courses from outside health care facilities, in-house cultures, and all antibiotic prescriptions. For those with positive urine cultures, species and antibiotic resistances were noted. Also, post-EF antibiotic strategies such as post-coital, self-start therapy, continuous daily antibiotic prophylaxis, or IV antibiotics were noted beginning 6 months after the EF procedure.

Descriptive statistics were provided as medians and interquartile ranges for continuous values and as frequencies and percentages for categorical values. Fisher's exact test was used to test for associations between categorical parameters and both the endoscopic outcome and clinical outcome. Student t-tests were used to analyze for differences in continuous values between endoscopic success and failure, and ANOVA was used for analyzing differences between the three clinical outcome groups. All tests were performed at the 0.05 significance level without adjustment for multiple comparisons using SAS 9.4 (SAS Institute Inc., Cary NC).

Result

Patient Characteristics: From 2008 to 2018, 40/514 women from our RUTI repository database met study criteria (Figure 2), including 34 in group 1 (endoscopic success) and 6 in group 2 (endoscopic failure). Baseline demographics and preoperative UTI management are shown in Table 1. Prior to the operation, 17 (43%) patients were on continuous suppressive antibiotics and 7 (18%) had required IV antibiotics for RUTI treatment. There were no statistically significant differences in patient characteristics or pre-operative UTI management between groups 1 and 2 (Table 1).

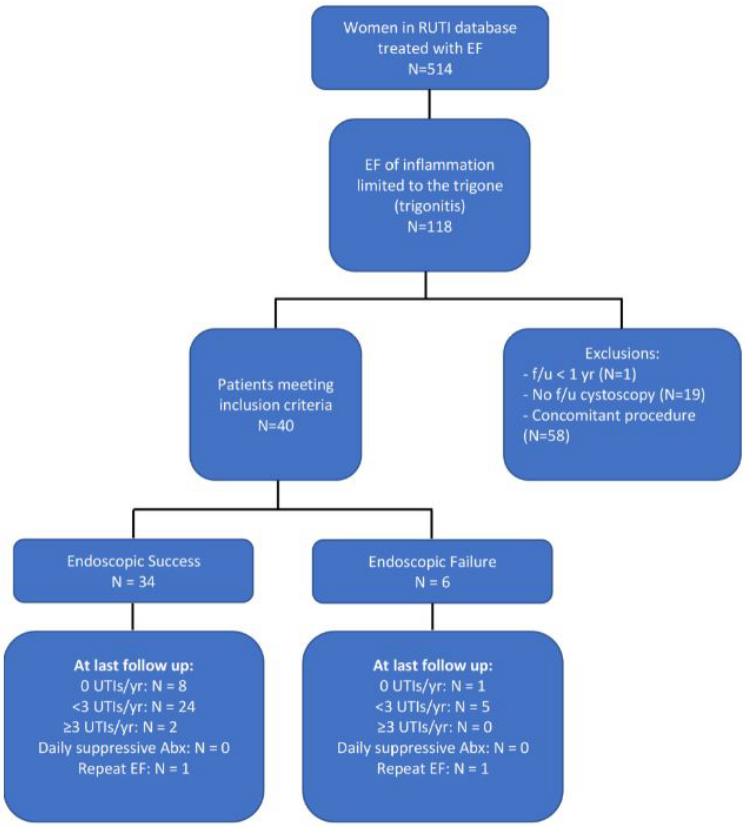

Figure 2: Patient Population

RUTI = recurrent urinary tract infections, EF = electrofulguration, f/u = follow up, Abx = antibiotics

Surgical Outcomes: The groups showed comparable procedure times (p=0.19), with almost all procedures lasting less than 25 minutes. No intra-operative or post-operative complications were noted. Most patients were considered endoscopically successful at their 6 months post-EF office cystoscopy (85%). Overall, 2/40 (5%) elected to pursue a second EF, including 1/34 (3%) from group 1 and 1/6 (17%) from group 2 (p=0.28).

Clinical Outcomes: Median follow-up in group 1 was 3.7 years (IQR 2.0-6.1) and 2.3 years (IQR 1.7-7.5) in group 2 (p=0.71). Median UTIs/year were comparable in both groups at 0.6 (0.2-1.1) for group 1 and 0.9 (0.3-1.6) in group 2 (p=0.89) (Table 1). The clinical outcomes were equivalent and overall, 9 (23%) were cured with 0 UTI/year, 29 (73%) were improved with <3 UTI/year and 2 (5%) failed with ≥3 UTI/year. After EF and prior to the 6-month follow-up cystoscopy, 15 patients were on suppressive antibiotics (5 for 6 weeks, 6 for 3 months, 7 for 6 months) to treat secondary infections during the healing of the trigone. But, after the post-EF cystoscopy at 6 months, no patients remained on long-term suppressive antibiotics. No difference was observed in post-EF cultures (strains and antibiotic resistances), nor in the use of post-EF post-coital prophylaxis, self-start antibiotics, IV antibiotics, or incidence of pyelonephritis between the two groups.

In the clinically improved group, 19 (66%) had <1 UTI/year in the follow-up period starting 6 months after EF. More patients with 1-2 or 2-3 UTIs/year utilized self-start antibiotics than those that had <1 UTI/year (p=0.0013). Table 2 shows full results of the clinically improved group with no other statistically significant differences.

Discussion

This study examined the role of EF in women with antibiotic-recalcitrant RUTIs and a negative thorough urological work-up for RUTIs other than evidence of inflammatory lesions limited to the trigone on office cystoscopy. During the follow-up period, trigonitis resolved in most, and many had substantial clinical improvement or cure of their RUTIs.

Endoscopic success was 85%, and very few patients underwent repeat EF, providing merit to the goal of the procedure of mechanically removing bacteria residing in the inflamed trigone. Many patients with both endoscopic success and failure had high levels of clinical cure or improvement. These clinical results were found consistent with another group that studied 9 years of clinical data and saw(a)significant reduction in UTIs for 12 months in 47 patients following cystoscopy with diathermy, a similar procedure to EF [23]. Since endoscopic success was classified as complete resolution of lesions, it is possible, though unproven, that some patients who had a few residual lesions, but a lesser burden than originally observed, experienced a reduction in their UTI recurrence rates and therefore still benefited from EF. Only two patients underwent a repeat fulguration, one from each group. The one person from the endoscopic success group that received a repeat fulguration developed new lesions elsewhere in the bladder years after the original procedure.

Although some patients continued to utilize other forms of antibiotic prophylaxis (post-coital or self-start therapy) after EF, no patients required continuous suppressive antibiotics after 6 months from EF, thus decreasing their antibiotic requirement that could have led to adverse effects or additional antibiotic resistance. Confirming our prior report, many patients in this optimal group of trigonitis alone required no additional antibiotic treatments after EF over a durable length of follow-up.

	<1 UTI/year (n = 19)	1-2 UTIs/year (n = 6)	2-3 UTIs/year (n = 4)	*P*
Median years of follow-up (IQR	6.0 (2.2-7.8)	2.5 (1.7-2.8)	5.0 (3.1-6.8)	0.059
Median age, years (IQR)	56 (46-64)	71 (56-83)	58(45-64.5)	0.16
Race				
White	18 (95%)	6 (100%)	4 (100%)	>0.99
Hispanic	1 (5%)	0(0%)	0 (0%)	
Median BMI (IQR)	26.6 (23.1-32)	27.9 (25.8-29.7)	28.4	(24-32.8)
Median Party (IQR)	2 (1-3)	2 (1-2)	2 (1-3)	0.77
Diabetic	2 (11%)	0 (0%)	0 (0%)	>0.99
Ever Smoker	7 (37%)	2 (33%)	1 (25%)	>0.99
Prior urologic Surgery	6 (32%)	1 (17%)	0 (0%)	0.56
Hysterectomy	10 (53%)	4 (67%)	3 (57%)	0.64
Menopause/oophorectomy	13 (68%)	5 (83%)	3 (75%)	0.84
HRT	9 (47%)	4 (67%)	3 (75%)	0.86
Sexually active	11 (61%)	3 (50%)	3 (75%)	0.74
Past Suppressive antibiotics	8 (42%)	2 (33%)	3 (75%)	0.55
Past post – coital prophylaxis	2 (11%)	1 (17%)	0 (0%)	>0.99
Past self-start	0 (0%)	0 (0%)	0 (0%)	
Past IV anitibiotics	3(16%)	1 (17%)	1 (25%)	>0.99
Past pyelonephritis	3 (16%)	1(17%)	1 (25%)	>0.99
Median length of surgery, min (IQR)	17 (15-21)	17.5 (14-22)	19 (14.5-21.5)	0.80
Post – fulguration outcomes				
Endoscopic failure	2 (11%)	3 (50%)	0 (0%)	0.070
Repeat fulguration	2 (11%)	0 (0%)	0 (0%)	>0.99
Post – fulguration Cultures				
E. coli	10 (53%)	3 (50%)	0 (0%)	0.74
Multiple Organisms	6 (32%)	3 (50%)	2 (50%)	0.62
Drug resistant	2 (11%)	1 (17%)	2 (50%)	0.17
FQ - resistant	2 (11%)	0 (0%)	1 (25%)	0.45
Bactrim - resistant	2 (11%)	2 (33%)	2 (50%)	0.094
ESBL	0 (0%)	1 (17%)	1 (25%)	0.11
Post – fulguration				
Post – coital prophylaxis	4 (21%)	3 (50%)	1 (25%)	0.41
Self – start antibiotics	0(0%)	2 (33%)	3 (75%)	0.0013
IV antibiotics	1 (5%)	1 (17%)	1 (25%)	0.27
Pyelonephritis	1 (5%)	1 (17%)	0 (0%)	0.58

Table 2: Patient characteristics by UTIs/year for clinically improved patients
Abbrevations: *IQR = Interquatile range, BMI = body mass index, IV = intravenous, UTI = urinary tract infections, ESBL = extended – spectrum beta –lactamase, FQ = fluroquinolone*

Further stratification of the clinically improved group showed that most patients with improvement had <1 UTI per year, indicating a significant reduction in disease burden and severity for these women who were consistently having ≥3 symptomatic UTI episodes per year. It was noted that more patients with 1-2 or 2-3 UTIs/year utilized self-start antibiotics than those that had <1 UTI/year.

EF is a short minimally invasive procedure associated with a low complication rate in our previous study and no peri-operative complication reported in this cohort [20]. While not currently recommended in the RUTI management guidelines, EF is utilized in other bladder pathologies such as interstitial cystitis with Hunner's ulcers [19] and in bladder tumor treatment in lieu of transurethral resection [24]. In all these instances, the superficial nature of the fulguration did not affect bladder function or compliance in the long run.

Other RUTI management strategies (continuous antibiotics, post-coital prophylaxis, self-start therapy, hormone replacement therapy) have been recommended with variable levels of success [7, 8]. A meta-analysis of 10 trials reported a decrease in UTI/year with 6-12 months of suppressive antibiotics compared to placebo (0-0.9 vs 0.8-3.6, respectively), but an increase in side effects was noted in the suppressive antibiotic group. Additionally, two studies in that analysis indicated no difference between suppressive antibiotics and placebo [25]. While long-term antibiotic administration can be effective, there are concerns about developing resistant bacterial strains [26]. Vaginal estrogen therapy has proven helpful in postmenopausal women but is limited by cost and compliance and does not help the premenopausal group [27,28]. Since chronic trigonitis is a localized regional condition in this subset of women with RUTI and considering the phenomenon of biofilm recalcitrance which protects these bacteria from anti-microbial treatment, EF may offer a durable benefit when other traditional forms of RUTI management have failed.

This study has many strengths including RUTI participants at the same stage of disease (limited trigonitis) to eliminate the confounding results of applying EF to various stages of more extensive cystitis. A subgroup analysis comparing those with

and without prior urologic surgery was performed, with both groups included in the overall analysis, extending the scope of our EF results. Based on EMR recordings, secondary UTI episodes after EF requiring antibiotic therapy were well-documented and included those with or without documented urine cultures, as expected from a real-life practice study with long-term follow-up data. Limitations of this study include its retrospective design at a tertiary care center, a predominant elderly, postmenopausal, and Caucasian population, limited pre-fulguration urine culture data, a limited sample size due to numerous exclusion criteria, and a small number of patients in the endoscopic failure group. Nonetheless, this subgroup of trigonitis-alone women with antibiotic-recalcitrant RUTI fared well enough with EF when compared to their traditional RUTI management before EF to invite a large scale, prospective and multicentric study to further explore the generalizability of these results. Thus far, our institution has had difficulty implementing a randomized controlled trial between EF and prolonged suppressive antibiotic therapy given difficulties with recruitment secondary to women not wanting to risk being assigned to the control arm (suppressive antibiotics) since they have been trying these antibiotics for years with little results and expressed concerns with long-term antibiotic side-effects.

Conclusion

In a cohort of women with antibiotic-recalcitrant RUTIs, found on cystoscopy to have inflammatory lesions limited to the trigone, EF resulted in resolution of trigonitis in the large majority of these women, along with clinical improvement or cure. As for other bladder pathologies, the role of EF in the management of these women warrants further investigation.

Acknowledgments

The authors thank Dr. Ramy Goueli for his comments and review of the manuscript.

References

1. Foxman, B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. American Journal of Medicine, 2002; 113 Suppl 1A:5S-13S.
2. Suskind, A. M., Saigal, C. S., Hanley, J. M., Lai, J., Setodji, C. M., et al. Incidence and Management of Uncomplicated Recurrent Urinary Tract Infections in a National Sample of Women in the United States. Urology. 2016; 90:50-55.
3. Gupta, K., Trautner, B. W. Diagnosis and management of recurrent urinary tract infections in non-pregnant women. BMJ. 2013;346:f3140.
4. Malik RD, Wu YR, Zimmern PE. Definition of Recurrent Urinary Tract Infections in Women: Which One to Adopt? Female Pelvic Med Reconstr Surg. 2018;24(6):424-429.
5. Gupta, K., Hooton, T. M., Roberts, P. L., Stamm, W. E. Patient-initiated treatment of uncomplicated recurrent urinary tract infections in young women. Annals of Internal Medicine. 2001; 135(1):9-16.
6. Wagenlehner, F., Wullt, B., Ballarini, S., Zingg, D., Naber, K. G. Social and economic burden of recurrent urinary tract infections and quality of life: a patient web-based study (GESPRIT). Expert Review of Pharmacoeconomics& Outcomes Research. 2016; 18(1):107-117.
7. Smith, A. L., Brown, J., Wyman, J. F., Berry, A., Newman, D. K., et al. Treatment and Prevention of Recurrent Lower Urinary Tract Infections in Women: A Rapid Review with Practice Recommendations. Journal of Urolog. 2018; 200(6):1174-1191.
8. Bonkat G, Pickard R, Bartoletti R et al. EAU guidelines on urological infections. 2017.
9. Tamadonfar, K. O., Omattage, N. S., Spaulding, C. N., Hultgren, S. J. Reaching the End of the Line: Urinary Tract Infections. MicrobiolSpectr. 2019; 7(3).
10. Malik, R. D., Wu, Y. R., Christie, A. L., Alhalabi, F., Zimmern, P. E. Impact of Allergy and Resistance on Antibiotic Selection for Recurrent Urinary Tract Infections in Older Women. Urology. 2018; 113:26-33.
11. Sihra, N., Goodman, A., Zakri, R., Sahai, A., & Malde, S. Nonantibiotic prevention and management of recurrent urinary tract infection. Nat Rev Urol. 2018; 15(12):750-776.
12. Yang, B., Foley, S. First experience in the UK of treating women with recurrent urinary tract infections with the bacterial vaccine Uromune((R)). BJU International. 2018; 121(2):289-292.
13. Stalenhoef, J. E., van Nieuwkoop, C., Menken, P. H., Bernards, S. T., Elzevier, H. W., et al. Intravesical Gentamicin Treatment for Recurrent Urinary Tract Infections Caused by Multidrug Resistant Bacteria. Journal of Urology. 2019; 201(3):549-555.
14. Klein RD, Hultgren SJ. Urinary tract infections: microbial pathogenesis, host-pathogen interactions and new treatment strategies. Nat Rev Microbiol. 2020;18(4):211-226.
15. Mulvey MA, Lopez-Boado YS, Wilson CL et al. Induction and evasion of host defenses by type 1 piliateduropathogenic Escherichia Coli Science. 1998; 282:1494-1497.
16. Engel, G., Schaeffer, A. J., Grayhack, J. T., Wendel, E. F. The role of excretory urography and cystoscopy in the evaluation and management of women with recurrent urinary tract infection. Journal of Urology. 1980; 123(2):190-191.
17. De Nisco, N. J., Neugent, M., Mull, J., Chen, L., Kuprasertkul, A., et al. Direct Detection of Tissue-Resident Bacteria and Chronic Inflammation in the Bladder Wall of Postmenopausal Women with Recurrent Urinary Tract Infection. Journal of Molecular Biology. 2019; 431(21):4368-4379.
18. Koo Y, Allan RN, Howlin RP, Stoodley P, Hall-StoodleyL. Targeting microbial biofilms: current and prospective therapeutic strategies. Nature Review. 2015; 15:740-755.
19. Hillelsohn, J. H., Rais-Bahrami, S., Friedlander, J. I., Okhunov, Z., Kashan, M., et al. Fulguration for Hunner ulcers: long-term clinical outcomes. Journal of Urology. 2012; 188(6):2238-2241.
20. Crivelli, J. J., Alhalabi, F., & Zimmern, P. E. Electrofulguration in the advanced management of antibiotic-refractory recurrent urinary tract infections in women. International Journal of Urology. 2019; 26(6):662-668.
21. Wu, Y. R., Rego, L. L., Christie, A. L., Lavelle, R. S., Zimmern, P. E, et al. Recurrent Urinary Tract Infections Due to Bacterial Persistence or Reinfection in Women-Does This Factor Impact Upper Tract Imaging Findings? Journal of Urology. 2016; 196(2):422-428.
22. Arbique GM, Gilleran JP, Guild JB, Harris JE, Zimmern PE, et al. Radiation exposure during standing voiding cystourethrography in women. Urology. 2006;67(2):269-274.
23. Chen, Z, Bates, L, West, N, Moore, K. A 9-year audit of the efficacy of diathermy for cystitis cystica. Urogynaecologia. 2019; 31:223.
24. Karakiewicz, P. I., Sun, M., &Azizi, M. Comparative effectiveness of transurethral resection of bladder tumors and office fulguration for recurrent bladder tumors. J Comp Eff Res. 2014; 3(2):131-133.
25. Albert, X., Huertas, I., Pereiro, II, Sanfelix, J., Gosalbes, V., et al.

Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane Database of Systematic Reviews. 2004; 2004(3):CD001209.

26. Ahmed, H., Davies, F., Francis, N., Farewell, D., Butler, C., et al. Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials. BMJ Open. 2017; 7(5):e015233.
27. Meister, M. R., Wang, C., Lowder, J. L., Mysorekar, I. U. Vaginal Estrogen Therapy Is Associated With Decreased Inflammatory Response in Postmenopausal Women With Recurrent Urinary Tract Infections. Female Pelvic Medicine & Reconstructive Surgery. 2019; 27(1):e39-e44.
28. Raz, R., &Stamm, W. E.A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. New England Journal of Medicine. 1993; 329(11):753-756.