

## Very Long-term Outcomes After Electrofulguration for Antibiotic-refractory Recurrent Urinary Tract Infections in a Predominantly Menopausal Cohort of Women

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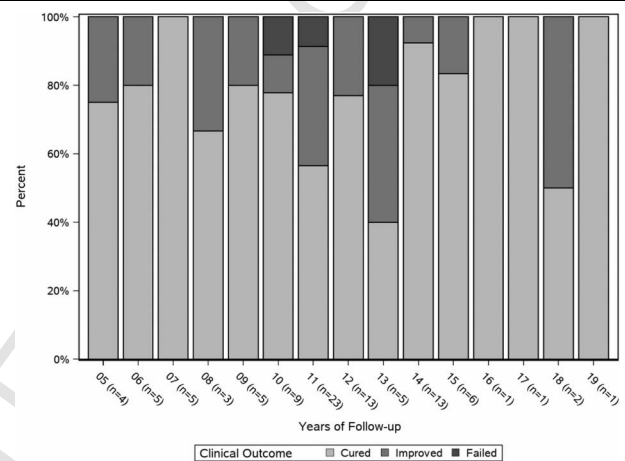
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**Study Need and Importance:** Antibiotic-refractory recurrent urinary tract infections (UTIs) are challenging to manage. Prior studies have shown that, in selected patients, electrofulguration (EF) of cystitis may disrupt potential nidus of recurrent UTI. We report on long-term outcomes of EF in women with at least 5 years of follow-up.

**What We Found:** From 2006 to 2012, 96 women met study criteria with median age 64. Median follow-up was 11 years (IQR: 10-13.5); 71 women had >10-year follow-up. The clinical outcome distribution by years of follow-up is displayed in the Figure. Prior to EF, 74% used daily antibiotic suppression, 5% used postcoital prophylaxis, 14% used self-start therapy, and 7% were not on prophylaxis. At last post-EF visit, 72% of women were cured, 22% improved, and 6% failed. Antibiotic usage decreased post-EF ( $P < .05$ ). Five percent were on continuous antibiotics at last follow-up as compared to 74% on continuous antibiotics pre-EF (McNemar  $P < .05$ ). Nineteen percent of women underwent a repeat EF.

**Limitations:** This study was conducted at a single, tertiary-care, academic center with mainly postmenopausal and Caucasian women and a potential referral bias to a Female Pelvic Medicine and Reconstructive Surgery-specialized practice, so generalizability may be limited. Given the length of the study period, there are also potentially confounding variables that may affect patient's UTI rates, including new onset of medical comorbidities



**Figure.** Distribution of clinical outcomes by years of follow-up.

(eg, diabetes, neurodegenerative conditions) that developed independently, as well as socio-environmental factors that may be difficult to capture.

**Interpretation for Patient Care:** In women with over 5 years of follow-up and beyond after EF for antibiotic-refractory recurrent UTIs, some were cured durably, whereas others sustained prolonged benefit with overall reduction in antibiotic usage. These long-term data can help guide management for women with challenging recalcitrant UTIs in whom chronic bladder inflammatory lesions observed on cystoscopy can be considered for fulguration.

## Very Long—term Outcomes After Electrofulguration for Antibiotic-refractory Recurrent Urinary Tract Infections in a Predominantly Menopausal Cohort of Women

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**Purpose:** Antibiotic-refractory recurrent urinary tract infections are challenging to manage. Prior studies have shown that, in selected patients, electrofulguration of cystitis may disrupt potential nidus of recurrent urinary tract infections. We report on long-term outcomes of electrofulguration in women with at least 5 years of follow-up.

**Materials and Methods:** Following Institutional Review Board approval, we analyzed a cohort of nonneurogenic women with  $\geq 3$  symptomatic recurrent urinary tract infections/y and inflammatory lesions on cystoscopy who underwent electrofulguration, excluding those with alternate identifiable etiology for recurrent urinary tract infections or less than 5-year follow-up. Preoperative characteristics, antibiotic regimens, and annual urinary tract infections were reported. Primary outcome was clinical cure (0-1 urinary tract infection/y), improvement ( $>1$  and  $<3/y$ ) or failure ( $\geq 3/y$ ) at last follow-up. Secondary outcomes included need for antibiotics or repeat electrofulguration. A subanalysis was performed for women with  $>10$ -year follow-up.

**Results:** From 2006 to 2012, 96 women met study criteria with median age 64. Median follow-up was 11 years (IQR: 10-13.5); 71 women had  $>10$ -year follow-up. Prior to electrofulguration, 74% used daily antibiotic suppression, 5% used post-coital prophylaxis, 14% used self-start therapy, and 7% were not on prophylaxis. At last post-electrofulguration visit, 72% of women were cured, 22% improved, and 6% failed. Antibiotic usage decreased post-electrofulguration ( $P < .05$ ). Five percent were on continuous antibiotics at last follow-up as compared to 74% on continuous antibiotics pre-electrofulguration (McNemar  $P < .05$ ). Nineteen percent of women underwent a repeat electrofulguration.

**Conclusions:** In menopausal women with over 5-year follow-up after electrofulguration for antibiotic-refractory recurrent urinary tract infections, there appears to be durable clinical cure and improvement, with decreased need for long-term antibiotics.

**Key Words:** postmenopause

RECURRENT urinary tract infections (RUTIs) are a challenging and burdensome condition for both patient and practitioner.<sup>1,2</sup> The 2019 AUA/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction Guidelines

for management of uncomplicated RUTIs offer a basic framework for initial management, including recommendation for prophylaxis and treatment with antibiotics, cranberry supplementation, and vaginal estrogens.<sup>3</sup> However, some

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Author Contributions: Conception and design: FA, PEZ; Data analysis and interpretation: SG, ALC, PEZ; Data acquisition: SG, PG, FA, PEZ; Critical revision of the manuscript for scientific and factual content: ALC, PG, FA, PEZ; Drafting the manuscript: SG, FA, PEZ; Statistical analysis: SG, ALC, FA, PEZ; Supervision: PEZ.

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women fail to improve with these initial management options and develop a more complex, chronic disease course. The consequences of long-term antibiotic usage are not insignificant, including development of antibiotic-resistant pathogens, hospitalization for parenteral antibiotic therapy, and systemic side effects of such medications. In a previous study, this subset of women with antibiotic-refractory RUTIs who had evidence of inflammatory bladder lesions on cystoscopic evaluation were confirmed on subsequent biopsies of these bladder lesions to harbor intramural resident bacterial reservoirs.<sup>4</sup> In addition, our group and others have studied the role of electrofulguration (EF) of these lesions to potentially clear the bladder of infection more durably, thus reducing future dependence on antibiotic therapy. EF has shown short- and mid-term promising efficacy in these patients in providing symptomatic relief, endoscopic resolution of lesions, and clinical reduction in urinary tract infections.<sup>4-7</sup>

Reviewing our institutional experience with this procedure over the past decade, we now report on long-term outcomes for women with over 5 years of follow-up after EF.

## MATERIALS AND METHODS

### Study Criteria

After Institutional Review Board approval, a prospectively maintained single-surgeon database of women with antibiotic refractory RUTI and cystoscopic evidence of chronic cystitis (cystitis cystica [Figure 1, A], vesicular cystitis) was reviewed by a third-party investigator not involved in the care of these patients. RUTI was defined as  $\geq 3$  symptomatic UTIs/y or  $\geq 2$  UTIs in 6 months with positive urine culture.<sup>8</sup> Antibiotic-refractory infection was defined as allergy or resistance to at least 3 classes of antibiotics.<sup>9</sup>

Women were excluded if they had less than 5 years of follow-up, uncontrolled diabetes, bothersome urinary incontinence, stage  $\geq 2$  prolapse, voiding dysfunction, post-void residual  $>100$  mL, neurogenic bladder, need for any form of catheterization, upper tract anomalies on imaging such as stone (US or CT) or prior major urological surgeries (ureteral reconstruction, fistula repair, augmentation cystoplasty), or ongoing chemotherapy or immunosuppression. Women were also excluded if EF was performed in conjunction with another urological procedure or if they had extensive inflammatory lesions beyond the trigone and bladder base.

### Cystoscopy and RUTI Evaluation

As part of their upper and lower urinary tract urological evaluation, women with antibiotic-refractory RUTIs underwent flexible office cystoscopy. A simple staging system has been used for some time to categorize the extent of the inflammatory lesions observed during cystoscopy, as follows: trigone alone (stage 1), trigone and bladder base (stage 2), bladder walls lateral to the ureteric orifices (stage 3), or diffusely involving the entire bladder (stage 4,

or pancystitis).<sup>7,10,11</sup> In this study, extensive lesions (stages 3 or 4) were excluded as stated above.

### EF Procedure

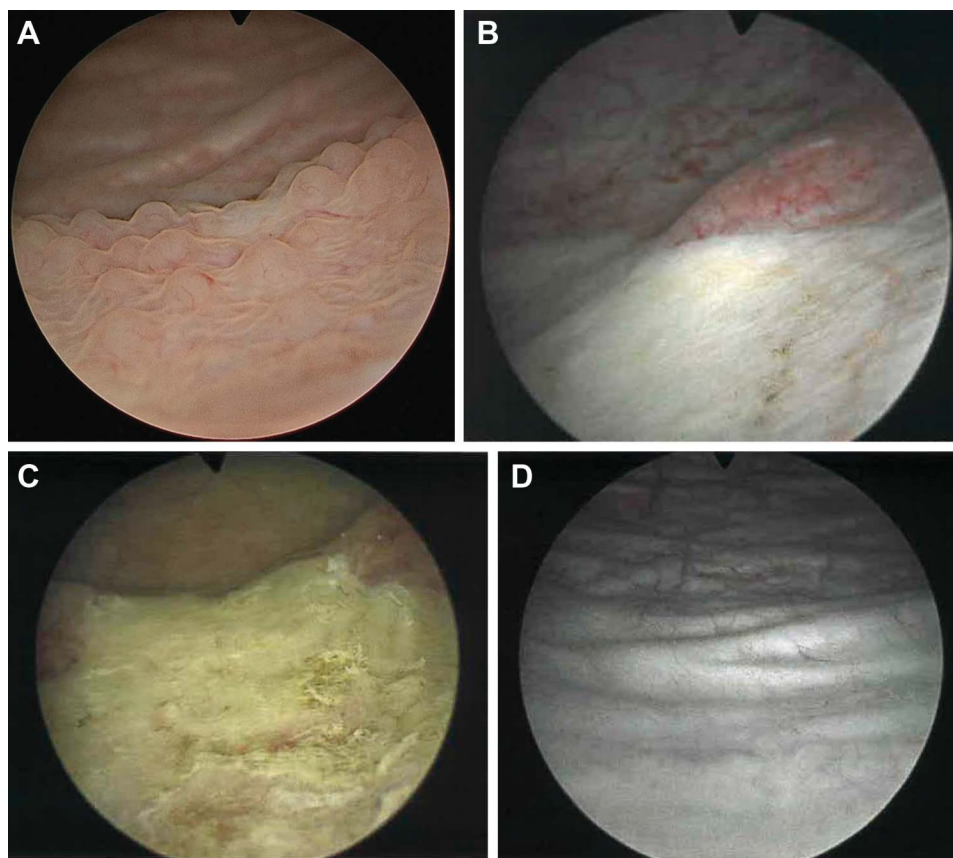
Due to lack of response to various antibiotic regimens, patients underwent outpatient EF of areas of chronic cystitis.<sup>12</sup> All EF procedures were done by a single surgeon on an outpatient basis. This procedure is classified as CPT code 52224. Anesthesia involved laryngeal mask airway or monitored anesthesia care, and rarely endotracheal intubation. A 17.5F female urethrocystoscope was used to inspect the bladder mucosa for inflammatory lesions of concern. Prior to fulguration, photos were obtained to delineate the extent of cystitis for staging purposes (Figure 1, A). Using a fine-tip monopolar Bugbee electrocautery on a low setting (20-25), the area of chronic cystitis (stage 1 or 2) was first marked out to define its boundaries and then superficially fulgurated. Following fulguration, photos were again obtained to document the result of fulguration (Figure 1, A and B). Patients were discharged home the same day. A low-dose daily antibiotic prophylaxis was recommended for the first 4-6 weeks post-EF to prevent an early post-EF UTI episode as the fulgurated area starts to heal.<sup>4,6</sup>

### Data Collection

Patient databases and Epic electronic medical record were reviewed starting at time of pre-EF office visit to time of most recent follow-up visit. Preoperative patient characteristics were reported including age, BMI, comorbidities, smoking status, parity, pre-EF antibiotic prophylaxis, and need for UTI-related hospitalizations to receive intravenous antibiotics. Number of UTI episodes in the 1 year preceding EF were recorded based on documented urine cultures with associated antibiotic treatment course. Operative report and photographs from the EF procedure were used to define disease stage.

Following EF, review of all electronically available documentation was performed including notes from all clinic visits (including primary care and urology specialist notes) and hospital encounters, patient communication with the clinic through MyChart via direct message or telephone encounters, records of any electronically prescribed medications (including antimicrobial or other prophylaxis) or laboratory results, as well as all clinical information from other institutions through CareEverywhere. Specifically, we recorded the number of annual culture-proven UTIs, time to repeat EF when indicated, additional testing or procedures performed, and usage of any antibiotic treatment (coital, daily continuous, self-therapy) both over the follow-up period post-EF and at the time of most recent follow-up visit.

The data set was queried for all women with over 5 years of follow-up after EF procedure. Patients were contacted for follow-up if they had been seen in clinics regularly for more than 5 years of follow-up but had not been seen in the past year, or if they had not been seen in follow-up in clinics up to a minimum of 5 years of follow-up, yet had their EF procedure done more than 5 years ago. Patients were contacted via standardized telephone interview to assess UTI symptoms, recurrent UTI episodes, additional procedures, and use of antibiotic (coital,



**Figure 1.** A, Chronic cystitis cystica stage 1 (trigonitis). B, Left side of the trigone just after fulguration (stage 2). C, Appearance of the whole trigone from the level of the bladder neck just after fulguration (stage 1). D, Six months after fulguration, healed trigone and bladder base areas (stage 2).

prophylaxis; see Supplementary Appendix 1, <https://www.jurology.com>). The questionnaire was administered by a trained third-party researcher not involved in the care of these women. All patients were contacted at least twice. From these patients, a subset of women with over 10 years of follow-up was also identified.

### Outcome Measures

Primary outcome was clinical status at time of most recent follow-up, defined as clinical cure (0-1 UTI/y), improvement ( $>1$  and  $<3$  UTI/y), or failure ( $\geq 3$  UTI/y).<sup>8</sup> Secondary outcomes included use of post-EF antibiotic prophylaxis, need for repeat EF procedure, and use of any additional nonantibiotic medications (ie, cranberry, D-mannose, phenazopyridine, vaginal estrogens, and probiotics). Outcomes prior to repeat EF were reported for patients who had repeat EF at least 5 years after their initial EF.

### Statistical Analysis

Descriptive statistics are provided as medians and interquartile ranges for continuous measures, and frequencies and percentages for categorical measures. The distribution of the clinical outcome by years of follow-up is visualized with a stacked bar chart. Antibiotic prophylaxis usage pre- and post-EF at time of last follow-up were compared with McNemar's test. Pre- and post-EF patient characteristics were analyzed for each post-EF clinical status group (cure, improved, or failed) using ANOVA statistical test for continuous patient

characteristics and Fisher's exact test for categorical characteristics. A similar secondary analysis of the post-EF patient characteristics was performed using the subset of patients with over 10 years of follow-up. We used Student *t* tests to analyze for differences between cystitis stages as well as between method of follow-up (clinic vs phone) for pre-/post-EF. We used Fisher's exact test to test for associations of cystitis stage or method of follow-up with categorical patient characteristics. All analyses were completed at the .05 significance level without adjustment for multiple comparisons using SAS 9.4 (SAS Institute Inc, Cary, North Carolina).

## RESULTS

### Patient Population

From 2006 to 2012, 202 women were identified who had antibiotic-refractory RUTIs and underwent cystoscopy with EF of chronic cystitis stages 1 or 2. Thirty-three were excluded as they underwent a simultaneous concomitant urological procedure (ie, prolapse repair, excision of vaginal mesh, sling placement). Forty-four women were excluded as they were deceased at time of data collection ( $n=29$ ) or had less than 5 years of follow-up reported in the chart ( $n=15$ ). Twenty-nine patients could not be reached via telephone interview due to no response or disconnected number.

**Table 1.** Patient Characteristics by Clinical Outcome

	Cured (n=71)		Improved (n=22)		Failed (n=3)		P value
Age, median (IQR), y	64	(52-72)	66	(58-75)	69	(63-78)	.2
Race, No. (%)							
Caucasian	62	(87)	22	(100)	3	(100)	.7
African American	4	(6)	0	(0)	0	(0)	
Asian	4	(6)	0	(0)	0	(0)	
Other	1	(1)	0	(0)	0	(0)	
BMI, median (IQR), kg/m <sup>2</sup>	25	(21.5-29.9)	26	(22-28.1)	21.5	(21.3-25.9)	.6
Parity, median (IQR)	2	(1-3)	2	(1-3)	3	(2-3)	.6
Diabetic, No. (%)	14	(20)	1	(5)	0	(0)	.19
Hysterectomy, No. (%)	46	(65)	14	(64)	3	(100)	.7
Menopause, No. (%)	61	(86)	21	(95)	3	(100)	.6
Hormone replacement therapy, No. (%)	34	(48)	14	(64)	2	(67)	.4
Sexually active, No. (%)	32	(45)	10	(45)	0	(0)	.4
Current smoker, No. (%)	8	(11)	1	(5)	0	(0)	.8
Pre-EF UTIs/y (range)							
Follow-up, median (IQR), y	11.2	(5-16)	11.1	(5-18)	11.4	(10-13)	

Abbreviations: BMI, body mass index; EF, electrofulguration; IQR, interquartile range; UTI, urinary tract infection.

Overall, 96 women met all study criteria with at least 5 years of follow-up (median 11 years for patients who have not failed), including 24 who were reached by telephone for a standardized interview. Of these, 71 women had over 10 years of follow-up. Patient characteristics are summarized in Table 1 and the clinical outcome distribution by years of follow-up is displayed in Figure 2.

### Paired Analysis of Antibiotic Management Pre- and Post-EF

At time of most recent post-EF follow-up visit, 72% of women met criteria for cured, 22% improved, and 6% failed with  $\geq 3$  UTIs/y. More women were not on an antibiotic management plan post-EF (61%) compared to pre-EF (22%; Table 2; McNemar  $P < .05$ ). At the last follow-up visit, 5% were on long-course continuous antibiotics as compared to 74% on continuous antibiotics pre-EF (McNemar  $P < .05$ ). Twenty-one percent used self-start therapy as needed, and 5% used postcoital prophylaxis, which did not differ significantly from pre-EF.

### Additional Post-EF Outcomes

Approximately 31% of women were on vaginal estrogen therapy at last follow-up, 15% on phenazopyridine for occasional dysuria, 22% on anticholinergics for urgency symptoms, 9% on cranberry supplements, and 6% on D-mannose for nonantimicrobial prophylaxis. Overall, 18 women underwent a repeat fulguration, with 82% refulguration-free survival at 10 years. Women with clinical failure were significantly more likely to have undergone a repeat EF intervention ( $P < .05$ ). After repeat EF, 50% (9/18) ultimately met the criteria for cured, 39% improved, and 11% failed.

Specifically in patients who met criteria for clinical cure, all also had endoscopic evidence of resolution of trigonitis on follow-up cystoscopy (Figure 1, D).

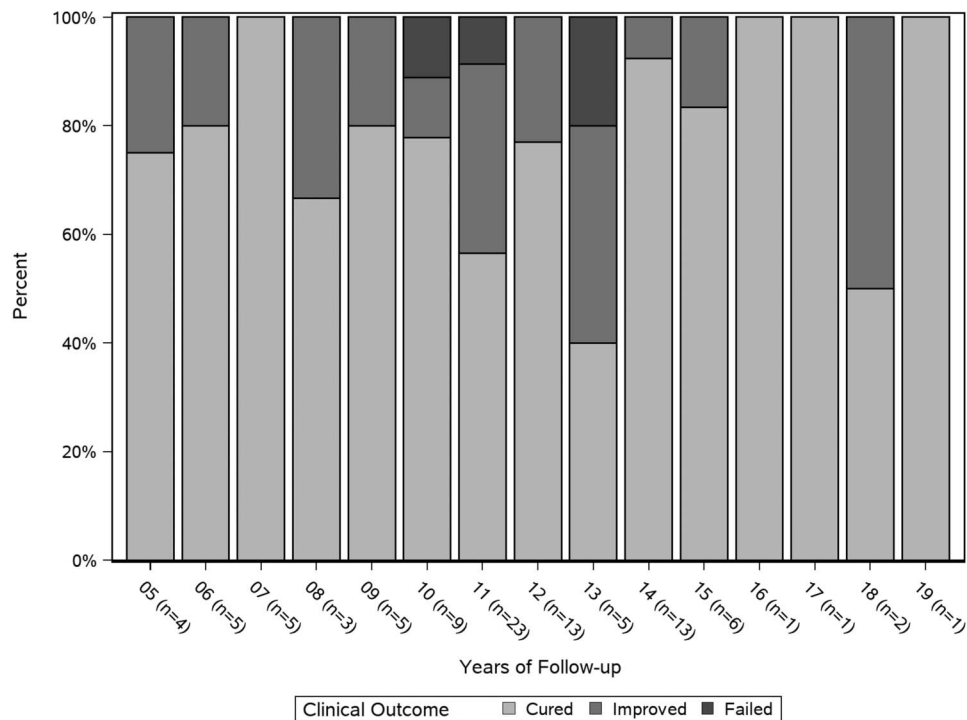
Seventy-eight percent were not on any antibiotic therapy at the time of last follow-up visit, whereas 22% still relied on self-start or postcoital therapy. In contrast, failed patients were more likely to rely on prophylaxis post-EF ( $P < .05$ ) and have endoscopic persistence of areas of bladder inflammation ( $P < .05$ ).

### Association of Patient Characteristics With Clinical Outcome Group, Cystitis Stage, and Follow-up Method

Comparing between post-EF clinical outcome groups (cured, improved, or failed), there was no significant difference in preoperative patient characteristics such as age, BMI, comorbidities, smoking status, parity, menopausal status, or sexual activity (Table 1). There was also no difference in type of pre-EF antibiotic prophylaxis regimen between groups, but post-EF, significantly more women in the cure group were not on any antibiotics (78% vs 19% in the improved group and 17% in the failed group, as summarized in Table 3). Among patients with stage 1 vs stage 2 cystitis, there was no significant difference between pre-EF characteristics or pre-EF antibiotic usage, and women with stage 2 cystitis were able to discontinue all antibiotic prophylaxis at a similar rate as with stage 1 cystitis (Table 4). Supplemental Table 1 (<https://www.jurology.com>) compares the patients who followed last in clinic vs over phone, and no significant differences were observed.

### Subgroup Analysis of Patients With 10 years of Follow-up

Examining the subset of women with over 10 years of follow-up, 70% of women were cured, 24% improved, and 6% failed (Table 3). Sixty-three percent of women were not on any antibiotic prophylaxis, while 18% used self-start therapy if needed, and 7% used postcoital prophylaxis. Six percent were on continuous antibiotic prophylaxis at time of last follow-up, in



**Figure 2.** Distribution of clinical outcomes by years of follow-up.

comparison to 76% from pre-EF (McNemar  $P < .05$ ). Approximately 28% of women utilized vaginal estrogen, 20% anticholinergics, 13% phenazopyridine, 8% cranberry supplements, and 8% D-mannose as adjunct therapies.

## DISCUSSION

In this study examining very long-term outcomes following cystoscopy with EF in women with antibiotic-refractory RUTI and cystoscopic evidence of inflammatory lesions confined to the trigone and/or bladder base (stages 1 or 2), we found durable clinical improvement. While not currently in the AUA or European Association of Urology guidelines, EF has been utilized by our group and others as a third-line

measure for women in whom UTIs recur despite exhausting prophylaxis and adjunct medical therapies. This study reviewing our institutional experience over the last decade supports that EF is safe, well tolerated, and may be able to help women remain UTI-free with minimal to no continued need for antibiotic involvement.

Antibiotic-refractory RUTIs can be a very challenging condition to manage, affecting patient's quality of life and impacting antibiotic usage and health care costs on a societal level. Among patients with RUTIs, our institution has previously reported allergy or resistance rates of 15%-33% to TMP-SMX, 15%-35% to fluoroquinolones, 5%-16% to nitrofurantoin, and 20% to all 3 classes.<sup>9,13,14</sup> Aside from allergic- or resistance-

**Table 2.** Comparison of Antibiotic Management Between Pre- and Post-electrofulguration

	Antibiotic management, No. (%)		Discordant antibiotic management, No. <sup>a</sup>		McNemar $P$ value
	Pre-EF	Post-EF	Only Pre-EF	Only Post-EF	
>5 y Post-EF (at last visit)					
Any antibiotic therapy	21 (22)	59 (61)	5	43	< .001
Self-start therapy	13 (14)	20 (21)	10	17	.18
Postcoital	5 (5)	5 (5)	2	2	> .9
Continuous	71 (74)	5 (5)	67	1	< .001
>10 y Post-EF (at last visit)					
Any antibiotic therapy	13 (18)	45 (63)	3	35	< .001
Self-start therapy	12 (17)	13 (18)	9	10	.8
Postcoital	3 (4)	5 (7)	1	3	.3
Continuous	54 (76)	4 (6)	51	1	< .001

Abbreviation: EF, electrofulguration.

<sup>a</sup> Discordant antibiotic management indicates the number of patients who did not have the same type of antibiotic management at pre- and post-EF; Only Pre-EF had the patients who were on the specific management at pre-EF but not post-EF, while Only Post-EF had the opposite.

**Table 3.** Antibiotic Usage by Clinical Outcome

	Cured (n=71)	Improved (n=22)	Failed (n=3)	P value
Pre-EF, No. (%)				
Continuous suppression	50 (70)	18 (82)	3 (100)	.4
Postcoital	4 (6)	1 (5)	0 (0)	> .9
Self-start therapy	9 (13)	3 (14)	1 (33)	.5
IV antibiotics	5 (7)	3 (14)	0 (0)	.5
Pyelonephritis	2 (3)	2 (9)	1 (33)	.049
Cystitis stage				.6
1	47 (66)	14 (64)	3 (100)	
2	24 (34)	8 (36)	0 (0)	
Post-EF, No. (%)				
Repeat fulguration	9 (13)	8 (36)	2 (67)	.0071
UTIs in first y				.019
0	51 (72)	10 (45)	1 (33)	
1	13 (18)	10 (45)	1 (33)	
2	6 (8)	2 (9)	0 (0)	
3	1 (1)	0 (0)	1 (33)	
>5 y Post-EF (at last visit), No. (%)				< .0001
None	55 (77)	7 (32)	1 (33)	
Self-start therapy	10 (14)	8 (36)	0 (0)	
Postcoital	3 (4)	3 (14)	0 (0)	
Short-course continuous (<3 mo)	3 (4)	3 (14)	0 (0)	
Long-course continuous (>3 mo)	0 (0)	1 (5)	2 (67)	
Cranberry	4 (6)	4 (18)	0 (0)	.16
Estrogen	19 (27)	10 (45)	0 (0)	.13
Phenazopyridine	9 (13)	2 (9)	1 (33)	.4
D-mannose	3 (4)	3 (14)	0 (0)	.3
Anticholinergics	17 (24)	2 (9)	1 (33)	.3
Endoscopic outcome				.0038
No lesions	71 (100)	19 (86)	2 (67)	
Persistent cystitis lesions	0 (0)	2 (9)	0 (0)	
Increased/more diffuse lesions	0 (0)	1 (5)	1 (33)	
Total cystoscopies, median (IQR)	3 (2-4)	4 (3-4)	4 (3-4)	.0091
No. visits, median (IQR)	8 (5-12)	9.5 (5-12)	8 (7-9)	.7
	Cured (n=50)	Improved (n=18)	Failed (n=3)	P value
>10 y Post-EF (at last visit), No. (%)				
None	38 (76)	8 (44)	1 (33)	< .01
Self-start therapy	9 (18)	4 (22)	0 (0)	
Postcoital	2 (4)	3 (17)	0 (0)	
Short-course continuous (<3 mo)	1 (2)	2 (11)	0 (0)	
Long-course continuous (>3 mo)	0 (0)	1 (5.6)	2 (66)	
Cranberry	3 (8)	3 (17)	0 (0)	
Estrogen	14 (28)	7 (39)	0 (0)	
Phenazopyridine	7 (14)	1 (5.6)	2 (66)	
D-mannose	3 (6)	3 (17)	0 (0)	
Anticholinergics	12 (24)	2 (11)	1 (33)	

Abbreviations: EF, electrofulguration; IQR, interquartile range; IV, intravenous; UTI, urinary tract infection.

related side effects, adverse implications of chronic antibiotic usage have been well documented. The US Food and Drug Administration released safety concerns regarding utilization of fluoroquinolones (eg, tendon rupture and nervous system interaction) and data from the American Geriatric Society and the Beers Criteria caution against chronic use of nitrofurantoin (eg, pulmonary and hepatic toxicity), thus pushing the AUA to advise against using these classes of medications for extended courses.<sup>15</sup>

In a subset of these women who suffer from RUTIs, chronic inflammatory bladder lesions can develop, and these have been confirmed to be their nidus for their recurrent infection pattern. Hence the role of EF to superficially eliminate these chronic infection sites. Cystoscopic evaluation of women with RUTI, while

previously thought to be unnecessary due to low incidence of detected malignancy, can identify these infection-related lesions in 60%-75% of patients, such as cystitis cystica or inflammatory polyps.<sup>10,16</sup> Studies in mice have demonstrated that some uropathogens are able to evade treatment and the host immune system by forming quiescent reservoirs within bladder epithelial cells, thus contributing to recalcitrant infections.<sup>17</sup> De Nisco et al demonstrated evidence of these intracellular resident bacterial reservoirs in such lesions via fluorescent in situ hybridization from bladder biopsies of women with antibiotic-refractory RUTI at time of EF.<sup>18,19</sup> A comparative study comparing bladder biopsies in women with antibiotic-recalcitrant trigonitis who underwent EF to those of healthy bladders and of active cystitis lesions examined other possible

**Table 4.** Pre-electrofulguration vs Post-electrofulguration Characteristics by Cystitis Stage

	Stage 1 (n=64)		Stage 2 (n=32)		P value
Age, median (IQR), y	64	(53.5-72.5)	67	(55-75.5)	.8
Race, No. (%)					.3
White	59	(92)	28	(88)	
Black/African American	1	(2)	3	(9)	
Asian	3	(5)	1	(3)	
Other	1	(2)	0	(0)	
BMI, median (IQR), kg/m <sup>2</sup>	25.2	(21.4-28.7)	25.3	(22.1-33.1)	.5
Parity, median (IQR)	2	(1-2)	2	(1-30)	.16
Diabetic, No. (%)	8	(13)	7	(22)	.3
Hysterectomy, No. (%)	43	(67)	20	(63)	.7
Menopause, No. (%)	56	(88)	29	(91)	.8
Hormone replacement therapy, No. (%)	36	(56)	14	(44)	.3
Sexually active, No. (%)	34	(53)	8	(25)	.0097
Current smoker, No. (%)	9	(14)	0	(0)	.027
Pre-EF, No. (%)					
Continuous suppression	46	(72)	25	(78)	.6
Coital	5	(8)	0	(0)	.17
Self-start	6	(9)	7	(22)	.12
IV antibiotics	7	(11)	1	(3)	.3
Pyelonephritis	5	(8)	0	(0)	.17
Repeat fulguration, No. (%)	14	(22)	5	(16)	.6
Long-term Post-EF (at last visit), No. (%)					
Long-term antibiotic usage					< .0001
None	38	(59)	25	(78)	
Self-start	13	(20)	5	(16)	
Post-coital	6	(9)	0	(0)	
Short course continuous	5	(8)	1	(3)	
Long course continuous	2	(3)	1	(3)	
Cranberry	6	(9)	2	(6)	.7
Estrogen	17	(27)	12	(38)	.4
Phenazopyridine	8	(13)	4	(13)	> .9
D-mannose	4	(6)	2	(6)	> .9
Anticholinergic	12	(19)	8	(25)	.6
Endoscopic outcome, No. (%)					> .9
No lesions	61	(95)	31	(97)	
Persistent cystitis lesions	1	(2)	1	(3)	
Increased/more diffuse lesions	2	(3)	0	(0)	
Total cystoscopies, median (IQR)	3	(2-4)	4	(2-4)	.8
No. of visits, median (IQR)	8	(5-11)	9	(6-12.5)	.3

Abbreviations: BMI, body mass index; EF, electrofulguration; IQR, interquartile range; IV, intravenous.

mechanisms of how EF may disrupt infections.<sup>11</sup> Uroplakins, a group of proteins that interact with type 1 pili of uropathogenic *Escherichia coli* and facilitate urothelial infection, was found to be decreased in healed areas of the bladder post-EF, impeding uropathogen attachment. This unique healing process may contribute to durable outcomes post-EF.

Our institution and others have previously reported on short-term outcomes following EF, demonstrating safety, reduction in overall UTI symptoms, and average UTIs per year, with mean follow-up ~48 months.<sup>5-7,12,16</sup> Similar findings were demonstrated by Chen et al using cystoscopy with diathermy, a form of fulguration, for antibiotic-refractory UTIs, and showed significant reduction in UTIs in the 12 months following the procedure.<sup>13</sup> Le et al examined a cohort of women with antibiotic-refractory RUTI who underwent EF to identify risk factors for development of future infections; in particular, women who were UTI-free in the first year after EF were more likely to remain UTI-free long-term.<sup>10</sup>

This study reports on our institutional experience with very long-term follow-up, with most patients having over 10 years of follow-up after EF. Telephone interviews were utilized to reach patients for more up-to-date symptom assessment when they had not been seen in the last year, and the Epic electronic medical record included review of all available cultures, imaging, office visits, and medications ordered through all associated health care systems. Nonetheless, one cannot exclude care at outside institutions not reported by the patients. This study was conducted at a single, tertiary-care, academic center with mainly postmenopausal and Caucasian women and a potential referral bias to a Female Pelvic Medicine and Reconstructive Surgery—specialized practice, so generalizability may be limited. Given the length of the study period, there are also potentially confounding variables that may affect patient's UTI rates, including new onset of medical comorbidities (eg, diabetes, neurodegenerative conditions) that developed independently, as well as socio-environmental factors



that may be difficult to capture. Certainly, this study did not consider RUTI women with more extensive stages of cystitis (stages 3-4), which have already been found to be more challenging,<sup>4,7</sup> nor factors like cost affordability of UTI management, or impact on quality of life including anxiety, depression, lost time from work, or sexual activity. Future studies should consider a randomized multi-institutional trial with a comparison group relying only on antibiotics, as previously attempted.<sup>4</sup>

## CONCLUSIONS

In women with over 5 years of follow-up and beyond after EF for antibiotic-refractory recurrent UTIs, some were cured durably, whereas others sustained prolonged benefit with overall reduction in antibiotic usage. These long-term data can help guide management for women with challenging recalcitrant UTIs in whom chronic bladder inflammatory lesions observed on cystoscopy can be considered for fulguration.

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## EDITORIAL COMMENT

Recurrent urinary tract infection (UTI) in females is a recalcitrant condition often frustratingly refractory to treatment. The plethora of treatments is a testimony that the therapeutic holy grail is yet to be found. One such treatment is electrofulguration of the bladder mucosa, which was first described in 1977.<sup>1</sup> The procedure is based on observing intracellular bacteria in bladder mucosal biopsies, prompting fulguration to eradicate these microbial sanctuaries. After a hiatus, electrofulguration is being explored again with evidence to suggest long-term efficacy.<sup>2</sup>

This paper retrospectively examines a single-center, single-surgeon experience in mostly menopausal women with antimicrobial refractory UTIs.<sup>3</sup> The authors limited their paper to patients with cystoscopic evidence of cystitis cystica or vesicular cystitis confined to the trigone and bladder base. They report long-term durability of cure in 72% and improvement in 22% of patients, with a consequent reduction in antimicrobial drug usage compared to before electrofulguration in 96 women followed for at least 5 years. Furthermore, their patients had cystoscopic evidence of resolution of trigonitis. It

must be noted, however, that patients were treated with 4-6 weeks of a low-dose antibiotic after the procedure. Additionally, nearly a third of the women were on topical estrogens, while a significant number needed to continue with agents providing symptomatic relief, such as phenazopyridine or D-mannose, amongst other methods, suggesting that while the cure rates were impressive, symptomatic relief lagged.

Apart from the study's retrospective nature, the element of recall via telephone interviews and possible treatments sought elsewhere are other limitations the authors accept. Previously, the same

group has presented results in more extensive forms of cystitis,<sup>4</sup> with results less impressive than in the present study.<sup>3</sup> Therefore, the exact role of electrofulguration needs to be defined further. Nevertheless, the authors' results suggest that the time for trials of electrofulguration for recurrent UTI has arrived.

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## REPLY BY AUTHORS

In follow-up on the comment by Dr Deepak Batura, one should be reminded that fulguration of the bladder is not a new concept. It has been applied broadly to the management of Hunner's ulcer<sup>1</sup> and bladder tumors. And in the case of antibiotic-refractory recurrent urinary tract infections (RUTIs), our group has proposed its use to eliminate chronic sites of infection in the bladder, not in the urethra.<sup>2</sup> Using a novel bladder-specific fluorescent in situ hybridization technology,<sup>3,4</sup> resident bacterial reservoirs were identified in biopsies of the trigone in postmenopausal women with RUTIs undergoing electrofulguration. Thus, given that antibiotics are known to be ineffective against these intracellular bacterial reservoirs, the ability of electrofulguration to cauterize and eliminate these superficial lesions offers an effective treatment

alternative for women with antibiotic-refractory RUTIs.<sup>5</sup>

Several of our publications related to electrofulguration have involved shorter-term follow-ups, thus prompting our interest to evaluate the unanswered clinical question of our very long—term results.<sup>2</sup> Certainly, women with pancystitis (stage 4) do fare worse than women with early stages (1, 2) with confined lesions to the trigone and/or bladder base due to a lesser extent of cystitis sites to fulgurate.<sup>6</sup> In that light, office flexible cystoscopy can assist in the detection of these early cystitis stages well suited for fulguration. With COVID-19, telephone interviews and outside care closer to home have become a reality of our daily tertiary practices and will remain a limitation forever. We fully agree that the time of trials has come.

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