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**IMPACT OF ALLERGY AND RESISTANCE ON ANTIBIOTIC SELECTION FOR
RECURRENT URINARY TRACT INFECTIONS IN OLDER WOMEN**

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Abstract:

Objectives

To review the impact of antibiotic allergy and resistance in older women with recurrent urinary tract infections (RUTIs) as determinants for a suitable oral antibiotic treatment choice.

Methods:

A prospectively maintained database of women 65 years old and older with documented RUTIs (≥ 3 UTI/year) and trigonitis on cystoscopy was reviewed. Demographic data, known drug allergies, renal function, antibiotic susceptibility of most recent urine culture, allergy and/or resistance to trimethoprim-sulfamethoxazole (TMP-SMX), fluoroquinolones, and nitrofurantoin were obtained.

Results

From 2006-2014, 86 women with RUTIs met study criteria. Mean age was 77.9 ± 7.8 with 94% being Caucasian. An eGFR >30 mL/min was noted in 94%. The percentage of women allergic, resistant, or both allergic and resistant to TMP-SMX was 33%, 29%, and 15%, to fluoroquinolones was 14%, 34%, and 8.1%, or nitrofurantoin was 16%, 14%, and 5% respectively. Twenty-eight percent (24/86) of women who were allergic and/or resistant to TMP-SMX and fluoroquinolones were sensitive to nitrofurantoin. Twenty percent (17/86) were allergic and/or resistant to all three antibiotics. Women who were allergic or resistant to TMP-SMX had a significantly higher number of other antibiotic resistances compared to women sensitive to TMP-SMX (4.9 ± 3.6 versus 2.1 ± 2.3 ; $p < 0.0001$). Similarly, women with fluoroquinolone allergy or resistance had significantly more antibiotic resistances than those who were fluoroquinolone sensitive (5.8 ± 3.5 versus 2.3 ± 2.5 ; $p < 0.0001$).

Conclusions

Due to allergy and/or antibiotic resistance, several first-line antibiotics are not available for many older women with RUTIs. In nearly a third of women, nitrofurantoin was the only viable alternative.

Legends:

Abbreviations

RUTI: Recurrent Urinary Tract Infection

UTI: Urinary Tract Infection

TMP-SMX: trimethoprim-sulfamethoxazole

eGFR: estimated Glomerular Filtration Rate

BUN: blood urea nitrogen

FDA: Food and Drug Administration

Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections in women with a lifetime risk of over 50%.¹ Recurrent UTIs (RUTI) are generally classified into two categories: those due to reemergence of the same bacteria (bacterial persistence), or due to new infections from outside the urinary tract (reinfection).² The most common

causative pathogen involved in RUTIs is *Escherichia coli*, accounting for approximately 80% of all infections. Other common pathogens include *Enterococcus* spp., *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, and *Proteus mirabilis*.³ Antimicrobial management for women with RUTI involves three strategies: low-dose prolonged continuous prophylaxis, self-start intermittent therapy, or post-coital prophylaxis.² In a 2004 Cochrane Review, recommended effective oral antimicrobial agents with minimal adverse effects included trimethoprim-sulfamethoxazole (TMP-SMX) or TMP alone, nitrofurantoin, or fluoroquinolones. Of those recommended antibiotic therapies for RUTI, recent data from the Beers Criteria have emerged cautioning against the use of long-term nitrofurantoin due to concerning side effect profiles.⁴ Additionally, based on warnings from the US Food and Drug Administration on “serious safety issues”, the American Urologic Association has recommended limiting use of fluoroquinolones when alternative treatment options are available.^{5,6} Therefore both nitrofurantoin and fluoroquinolones for acute infections are currently under intense scrutiny for use in the management of RUTI.

In addition to drug-induced adverse events, the management of RUTI has increased in complexity due to growth of antimicrobial resistance and presence of antimicrobial allergies. The development of antimicrobial resistance has been found to be due to a number of mechanisms including alterations of drug targets, augmentation of drug efflux, movement of antibiotics out of cells, or decreasing drug permeability. This can occur due to chromosomal point mutations and plasmid-mediated genes which can exchange between strains of the same or different species. Ultimately, treatment with

antibiotics with high resistance rates leads to selective pressures where resistant strains survive and results in increased prevalence.^{7,8}

The prevalence of adverse drug reactions in the general population has been estimated to be from 6 to 15% and of those approximately 6 to 10% are considered allergic drug reactions.⁹ However, higher rates of antibiotic allergies have been reported in patients of female gender, with increasing age, and in patients with higher historical use of antibiotics.¹⁰

Due to the complexities associated with antimicrobial treatment of RUTI, we sought to review our experience with a cohort of older women with RUTI and recognized trigonitis treated at a tertiary care center to examine the impact of antibiotic allergy and resistance on antibiotic selection in their care.

Methods

We reviewed an institutional review board approved, prospectively maintained database of ≥ 65 years old women with RUTIs and cystoscopy-proven trigonitis. Trigonitis is defined as chronic mucosal inflammation of the trigone.¹¹ Previous reports have shown approximately half of women with RUTIs will have findings of trigonitis on cystoscopy.¹² We selected this subgroup of women with RUTI for two reasons. First, they exhibit chronic changes in the trigone which could be the source of their recurrent infections. Second we have observed improvement or cure of RUTIs with fulguration of trigonitis observed on cystoscopy, the subject of additional study. RUTI was defined as 3 or more uncomplicated UTIs in 12 months documented on urine culture with a midstream urine bacterial count of at least 1×10^5 CFU/L¹³ for each culture while the patient was

symptomatic..¹³ UTI symptoms included dysuria, frequency, urgency, and/or suprapubic pressure/pain.² Urine cultures containing three or more bacterial species were considered as contaminants and excluded. Excluded were women with a known etiology of RUTIs (complicated RUTIs) such as women who performed clean intermittent catheterization, those with an indwelling catheter, and those with a history of pyelonephritis, nephrolithiasis, hydronephrosis, greater than stage 2 anterior compartment prolapse or a neurogenic bladder. Data was acquired through an electronic medical record (EPIC) by a reviewer (YW) not involved in patient care. Data originated from a Urology clinic dedicated to Female pelvic medicine and reconstructive surgery referrals. Data collected included: demographic data including race, BMI, age, gravidity, parity, prior urine culture results, diabetic status, immunosuppression status (corticosteroids, immunosuppressant medications or chemotherapy), menopausal status, sexual activity, hormonal replacement status, smoking status, prior surgeries, history of pyelonephritis and nephrolithiasis, known drug allergies as well as antibiotic allergies, blood urea nitrogen (BUN), creatinine, estimated GFR (eGFR), and antibiotic susceptibility profile. BUN, creatinine, and eGFR were taken from the most recent available metabolic panel testing, duration of RUTIs was based on patient report, and antibiotic susceptibility profiles were taken from the most recent urine culture. Bacterial persistence (same strain) and reinfection (differing strains) were analyzed based on bacterial strains between the most recent urine culture and the one prior. Three commonly used antibiotics for the management of RUTIs were further analyzed in regards to allergy and bacterial resistance, and those were: trimethoprim-sulfamethoxazole (TMP-SMX) and other sulfonamides, fluoroquinolones (ciprofloxacin,

levofloxacin, moxifloxacin), and nitrofurantoin. These antibiotics were selected after review of contemporary guidelines for the treatment of women with RUTI.

(Supplementary Table 3). Sensitivity to an antibiotic was defined as notation of sensitive (S) on the urine culture antibiotic sensitivity testing results.

Statistics

Descriptive statistics were reported for continuous and categorical variables using the mean $\pm$ SD and frequency and percentage, respectively. The Fisher exact test and Students t-test were utilized for comparison of continuous and categorical variables. Specifically, the characteristics of patients with antibiotic allergies, resistances both, or sensitivity were analyzed and the mean number of allergies and resistances between patients with and without co-existing TMP-SMX, fluoroquinolone and nitrofurantoin allergies and or resistances were compared. All analyses were performed using SAS®, version 9.4.

Results

From 2006 to 2014, 86 of 168 (51%) women with RUTI met study criteria. Eighty-two women were excluded, including 63 with age less than 65 years old and 19 with incomplete antibiotic susceptibility profile to review in the EMR. For all included patients the mean age was 77.9 ± 7.8 with 94% (81/86) being Caucasian. Average BMI was 24.4 ± 6.1 . Ten percent (9/86) of patients had a diagnosis of type 2 diabetes mellitus. Mean BUN and creatinine were 17.3 ± 8.3 mg/dL and 0.84 ± 0.29 mg/dL, respectively. eGFR >60 mL/min was noted in 65% and eGFR >30 mL/min in 94%. (Table 1) From the most recent urine culture analyzed, the most common bacterial strain isolated was

E.coli (55.8%), followed by *Enterococcus spp.* (18.6%) and *Klebsiella pneumoniae* (14%) (Supplementary Table 1). Seven percent of women had UTI with two bacterial strains. UTIs were due to bacterial persistence in 43% and bacterial reinfection in 46.5% of women. Mean number of known allergies to all medications (including antibiotics) was 3.5 ± 3.9 and to only antibiotics was 1.6 ± 1.8 . Women who were allergic to TMP-SX, fluoroquinolones, and nitrofurantoin were significantly more likely to have on average one additional antibiotic allergy in comparison to women who did not have allergies. (Supplementary Table 2). Manifestations of drug allergies to fluoroquinolones, nitrofurantoin and sulfonamides are listed in Table 2. The mean number of antibiotic resistances was 4.3 ± 3.5 . Sixty-two women (72%) had available data on duration of RUTIs by patient report. Of those, 55% (34/62) had RUTIs for ≤ 5 years and 45% (28/62) had RUTIs for > 5 years.

Included patients were evaluated in 4 groups, those with allergies alone, resistance alone, both allergies and resistance to, or sensitivity to antibiotics. The percentage of women who were either allergic and/or who had resistance to TMP-SMX, fluoroquinolones, or nitrofurantoin was 77% (66/86), 56% (48/86), and 35% (30/86), respectively. (Table 3) Twenty-eight percent (24/86) of women who were allergic and/or resistant to TMP-SMX and fluoroquinolones were neither allergic nor resistant to nitrofurantoin. Of these 24 women, only 1 had eGFR < 30 mL/min that would preclude her from receiving nitrofurantoin. Twenty percent (17/86) were allergic and/or resistant to all three antibiotics. There was no significant association with the presence of antibiotic allergy, resistance or sensitivity based on patient age, ethnicity, presence of diabetes or duration of RUTI. Women who were either allergic or resistant to TMP-SMX

had a significantly higher number of other antibiotic resistances compared to women that were sensitive to TMP-SMX (4.9 resistances ± 3.6 versus 2.1 ± 2.3 ; $p < 0.0001$). Similarly, women with either fluoroquinolone allergy or resistance had significantly more antibiotic resistances than those that were fluoroquinolone sensitive (5.8 resistances ± 3.5 versus 2.3 ± 2.5 ; $p < 0.0001$). However, there was no significant difference in number of antibiotic resistances in women with nitrofurantoin allergy or resistance compared to those who were nitrofurantoin sensitive (4.5 ± 3.0 versus 4.2 ± 3.8 ; $p = 0.70$).

Discussion

The management of RUTIs in older post-menopausal women is often complicated by the interplay between antibiotic allergy and resistance, risk of drug-induced adverse reactions, and antibiotic side effect warnings issued by influential organizations such as the American Geriatric Society, the American Urological Association, and the U.S. Food and Drug Administration. While numerous studies around the world have studied antimicrobial resistance rates, few include information on antibiotic allergy. Based on previously published series summarized in Table 4, reported resistance rates vary widely depending on the studied geographic location, time frame, ethnicity, and age group.; resistance rates for TMP-SMX range from 16% to 96%, for fluoroquinolones from 5.5% to 60%, and for nitrofurantoin from 1.1% to 14%.^{14–18} While the trend of nitrofurantoin having significantly lower resistance rates than the other two categories of antimicrobial agents is seen in numerous studies,^{14,17–20} resistance rates have been increasing with time for all three antibiotics.

The purpose of this study was to evaluate the rate of allergy and antimicrobial resistance to commonly utilized antibiotic therapies for the management of RUTIs in older women^{2,21-24}. We found 28% of women with RUTIs had only nitrofurantoin available as an oral antibiotic option due to allergy and/or antibiotic resistance to TMP-SMX and fluoroquinolones. All but one of those women would have been eligible to be treated with it. Also, women were equally likely to be sensitive to nitrofurantoin regardless of the number of other antibiotic allergies/resistances or sensitivity to TMP-SMX/fluoroquinolones. This was not the case for TMP-SMX and fluoroquinolones; women with either allergy and/or resistant to TMP-SMX or fluoroquinolones had significantly more antibiotic resistances than those who were not. Interestingly, the duration of the RUTI was not a significant determinant of antibiotic susceptibility however this may be due to the limited number of patients with self-reported duration of RUTI greater than 5 years.

Antimicrobial-resistant RUTIs have increased in both frequency and spectrum in the hospital and community. Bacterial selective pressure due to pervasive antimicrobial use, transmission of drug resistance between pathogens, and other microbial characteristics, such as expression of extended spectrum β -lactamases or carbapenemases, all have contributed to this increased resistance.²⁵ Factors that may influence antimicrobial resistance on an individual basis are advanced age, travel history, chronic medical conditions, recent hospitalizations, and recent antibiotic courses. Increasing age has been previously correlated with an increasing number of antimicrobial resistant rates in urinary isolates. A study by Gobernado et al. found resistance rates for ciprofloxacin were higher in women aged >65 years compared with those aged 18-65 years and

prevalence of resistance to multiple antimicrobials was also statistically higher in the elderly group.¹⁴

Furthermore, microbe resistance can vary widely based on geographic location. Such community-based variation was analyzed in the SENTRY Antibiotic Surveillance Program, which consisted of 31 medical centers in North America; Mathai et al. found significant differences in antimicrobial resistance patterns among geographic areas and emphasized the need for continued surveillance studies to establish baseline antimicrobial resistance by geographic location.²⁶

Existing literature on allergies associated with antibiotic use is limited. Incidence and prevalence rates of antibiotic allergies have been extrapolated from analysis of a large outpatient electronic medical record in San Diego county, CA, with demographics similar to that of the general population with health care coverage.¹⁰ Incidence rates of male and female patients with sulfa antibiotic allergy were 2.23% and 2.42% and quinolone antibiotic allergy was 0.52% and 1.01%, respectively. Prevalence rates for antibiotic allergy to sulfas and quinolones was 5.4% and 0.6%, respectively. Female patients reported significantly higher rates of antibiotic allergy in every decade of life in comparison to male patients except within the first decade of life. Older patients also reported greater rates of antibiotic allergy in all drug classes. Interestingly, they found that female patients used significantly more total antibiotics per year compared to their male counterparts. Based on this data, older female patients are most likely to utilize antibiotics and have antibiotic allergies compared to all other patients with over 20% of women over age 80 reporting an allergy to sulfa-class antibiotics. Similarly, other

studies in Portugal and Canada report greater rates of drug allergies in women in comparison to their male counterparts.^{27,28}

In regards to antibiotic side effects, there have been warnings from prominent organizations regarding the use of certain first-line RUTI antibiotic choices. In the most recent Beers Criteria for potentially inappropriate medication use in older adults (2015), Nitrofurantoin was mentioned as a concern in the treatment of RUTIs in older women because of the “potential of pulmonary toxicity, hepatotoxicity, and peripheral neuropathy, especially with long-term use.”⁴ Therefore, the current recommendation was to use safer alternatives when possible and avoid use in individuals with creatinine clearance <30 mL/min. Nitrofurantoin was not recommended for long-term bacterial suppression. Nevertheless, the results of our study suggest that nitrofurantoin remains an important antibiotic option in the management of RUTIs in older women along with careful monitoring for rare, but potentially serious adverse events.²⁹ This information should be useful to geriatricians and primary care providers managing older women with this condition. While nitrofurantoin and fluoroquinolones are under scrutiny in the general population to minimize the risk of increasing resistance patterns, our data indicates their utility in the management of complex older women with RUTIs who have allergies and/or resistance to multiple antibiotics.

A recent FDA review found that systemic fluoroquinolones (oral or injectable) were associated with “disabling side effects involving tendons, muscles, joints, nerves and the central nervous system,” therefore their use in uncomplicated urinary tract infections should be reserved when no alternative treatment option exists.^{5,6} After the dated their safety labeling regarding the use of fluoroquinolones, the American Urological

Association (AUA) released a statement supporting the use of fluoroquinolones with the caveat that it “should not be considered first line unless there is a contraindication to recommended first line therapies.”³⁰ However, no specific comments were made regarding our population involving post-menopausal women with RUTIs.

The strengths of our study included our ability to evaluate antibiotic susceptibility and distinguish antibiotic allergy and resistance for the three most commonly used first-line management options for RUTIs. Limitations of our study included observational data from a single tertiary care institution in a specialty urology clinic which may not only limit the generalizability but also may not reflect the allergy/antimicrobial resistance patterns of other communities with differing local susceptibilities and patient populations. The antimicrobial resistance patterns presented are from the patient’s most recent culture which may change with evolving patterns of antibiotic resistance with time. Additionally, our rate of allergies is higher than the general population; this may be due to several factors including age of the population, exposure to multiple antibiotic courses, and/or selection bias.. Furthermore, these well-characterized and thoroughly studied women had confirmed trigonitis on office cystoscopy, a common finding previously reported in over half of women with RUTIS.¹² Because of these restrictive inclusion criteria, the sample size, although large for this condition, can be deemed relatively small compared to all women with RUTIs. Finally, our study was comprised of primarily older Caucasian women, so our conclusions may not be applicable to other patient populations with differing demographics.

Conclusion

Due to allergy and/or antibiotic resistance, several first-line antibiotic options are not available for many post-menopausal Caucasian women with RUTIs. Twenty percent of women were allergic and/or resistant to all three antibiotics. In nearly a third of women, nitrofurantoin was the only remaining choice for management in these complex patients.

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Table 1: Demographic Data of Included Patients with RUTI

Mean age (years $\pm$ SD)	77.9 $\pm$ 7.8
Mean Body Mass Index (kg/m ² $\pm$ SD)	26.5 $\pm$ 6.0
Race	
Caucasian (n(%))	81 (94%)
Other (n(%))	5 (6%)
Diabetic	9 (10%)
Renal Function	
Mean BUN (mg/dL $\pm$ SD)	17.3 $\pm$ 8.3
Mean Creatinine (mg/dL $\pm$ SD)	0.84 $\pm$ 0.29
Mean eGFR (mL/min/1.73 m ² $\pm$ SD)	57.2 $\pm$ 8.5
UTI duration > 5 years (n/total(%))	28/62 (45%)

Table 2 : Manifestations of Drug allergy

Type of Allergy	Fluroquinolones (n=19)	Nitrofurantoin (n=18)	Sulfonamides (n=41)
Anaphylaxis	1 (5)	0 (0)	1 (2)
Angioedema	1 (5)	1 (6)	5 (12)
GI Disturbance	5 (26)	4 (22)	2 (5)
Hives	1 (5)	0 (0)	5 (12)
Pulmonary Side Effect	0 (0)	2 (11)	0 (0)
Pruritis	1 (5)	2 (11)	2 (5)
Rash	2 (11)	2 (11)	5 (12)
Respiratory Distress	1 (5)	1 (6)	4 (10)
Tendinitis	1 (5)	0 (0)	0 (0)
Other*	6 (32)	6 (33)	17 (41)

*Other includes anemia, tachycardia, possible drug induced lupus, unspecified intolerance, syncope, dizziness, fever and burning sensation in the bladder

Table 3: Main demographic parameters related to antibiotic allergy and/or resistance findings, N=86

	Allergy Only	Resistant Only	Both Allergy and Resistant	Antibiotic Sensitivity	<i>p</i>
TMP-SMX*	28	25	13	20	
Mean age, years	77±7	77±7	82±8	77±8	0.17
White	26 (93)	22 (88)	13 (100)	20 (100)	0.41
Diabetic	5 (18)	1 (4)	1 (8)	2 (10)	0.48
Duration 5+ years	10/21 (48)	7/21 (33)	5/8 (63)	6/12 (50)	0.53
Fluoroquinolone**	12	29	7	38	
Mean age, years	75±7	79±7	82±9	78±8	0.29
White	11 (92)	29 (100)	7 (100)	34 (89)	0.22
Diabetic	0 (0)	1 (3)	2 (29)	6 (16)	0.09
Duration 5+ years	3/10 (30)	12/21 (57)	1/5 (20)	12/26 (46)	0.37
Nitrofurantoin	14	12	4	56	
Mean age, years	79±9	77±5	81±10	78±8	0.77
White	13 (93)	12 (100)	3 (75)	53 (95)	0.31

Diabetic	0 (0)	0 (0)	1 (25)	8 (14)	0.16
Duration 5+ years	6/13 (46)	3/10 (30)	3/3 (100)	16/36 (44)	0.24

*Trimethoprim-sulfamethoxazole

**Includes ciprofloxacin, levofloxacin, and moxifloxacin

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Table 4: Summary of Published Antimicrobial Resistance to Urinary Tract Infections

Source	Year	Location	n	Age	Gender	Type of UTI	Pathogen	Resistance		
								TM P-SX (%)	F (%)	N (%)
Zhanel et al. ¹⁷	2006	USA/Canada	1,142	All	M/F	Outpatient	<i>E.coli</i>	21.3	5.1 - 5.5	1.1
Gobernado et al. ¹³	2007	Spain	2,292	18+	F	CA	<i>E.coli</i>	NR	18.2 - 18.4	6.2
			1500	>65				NR	28.8	4.1 - 10.5
Cullen et al. ¹⁶	2011	Dublin, Ireland	23,838	All	M/F	CA	<i>E.coli</i>	32.1	10.6	2.1
			15,398			HA		36.3	17.8	2.9
			2,797			Urological pts		35.5	28.6	5.8
Khawcharoenporn et al. ²⁸	2012	Chicago, IL USA	337	All	M/F	CA	<i>E.coli</i>	21	10	4
							All	17	10	9
						HA	<i>E.coli</i>	39	39	4
							All	26	38	9
Swami et al. ²⁹	2012	Minnesota, MN USA	5,619	All	M/F	<i>E.coli</i>	<i>E.coli</i>	17-25	7-16	NR
Kahlmetz and Poulsen ¹⁹	2012	Europe †	1,697	18 - 65	F	CA, acute, uncomplicated, non-RUTI,	<i>E.coli</i>	14.4 - 18.2	0.5 - 7.6	<2
Linhares et al. ³⁰	2013	Portugal	18,797	All	M/F	Clinical UTI, post-treatment UTI, pregnant women with UTI	<i>E.coli</i>	25.4	13.7 - 14.4	6
							<i>P. mirabilis</i>	41.5	21.3 - 22.9	95.1
							<i>Klebsiella</i>	36.	21.	32.

							<i>sp.</i>	0	7-22.9	8
							<i>S. aureus</i>	15.6	17.8-21.1	-
							<i>E. faecalis</i>	35.5	38.1-45.1	8
							<i>S. epidermidis</i>	25.9	25.5-26.6	-
McGregor et al. ¹⁸	2013	Western USA	2,274	All	M	Outpatient <i>E.coli</i>	<i>E.coli</i>	13.7	6.8	3.6
			32,265		F			15.3	4.1	2.4
Tandogdu et al. , ¹⁴	2014	Multi-national	1,866	All	M/F	HA in urological pts	<i>E.coli</i>	48	45	-
							<i>Klebsiella sp.</i>	62	57	-
							<i>Proteus sp.</i>	55	30	-
							<i>Enterobacter sp.</i>	52	42	-
							<i>P. aeruginosa</i>	96	64	-
							<i>Enterococcus sp.</i>	62	69	-
							CoNS	55	60	-
							<i>S. aureus</i>	26	54	-

M = male, F = Female, †Austria, Greece, Portugal, Sweden and the UK, CA = community acquired, HA = hospital acquired, pts = patients CoNS = coagulase-negative staphylococci, *E.coli* = *Escherichia coli*, *P. mirabilis* = *Proteus mirabilis*, *S. aureus* = *Staphylococcus aureus*, *E. faecalis* = *Enterococcus faecalis*, *S. epidermidis* = *Staphylococcus epidermidis*, *P. aeruginosa* = *Pseudomonas aeruginosa*,

EDITORIAL COMMENT

Re: "IMPACT OF ALLERGY AND RESISTANCE ON ANTIBIOTIC SELECTION FOR RECURRENT URINARY TRACT INFECTIONS IN OLDER WOMEN"

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A small prospective database inquires into the limitations of empiric antibiotic choice for recurrent UTIs in the setting of emerging resistance patterns and the often overstated patient reported "allergies.". This work brings up several clinical points. Drug provocation testing by allergists might clarify the situation for many, particularly appropriate for those at high-risk for a complicated UTI. However, while it is not uncommon that a patient's self-reported "allergies" lead to their refusal to take an appropriately indicated antimicrobial, the use of quinolones as first line empiric treatment is wrong for the selfsame reason, its adverse event profile!¹ First

References:

line empiric treatment is not quinolones, it remains trimethoprim-sulfamethoxazole, or nitrofurantoin². The Beer Criteria concerns itself with long-term nitrofurantoin suppression and with the inappropriate use with Creatinine Clearances > 30 mL/min.³⁴ Perhaps the largest issue, completely unaddressed at this time, is why physicians continue to treat a largely self-limited, organ confined and non-life threatening illness with systemic antimicrobials. Work should be encouraged to address this problem.

¹ Tennyson LA and Averch TD. Update on Fluoroquinolones: emergence of Multisystem Toxicity Syndrome. *Urology Practice* 4(5); 383-387, 2017.

² Hooton TM. Uncomplicated Urinary Tract Infection. *NEJM* 366(11), 1028-37, 2012.

³ Griebing TL, Dineen MK et al. AUA White Paper on the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *Urology Practice* 3(2), 102-111, 2016.

⁴ American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 63(11), 2227-46, 2015.

AUTHOR REPLY TO EDITORIAL COMMENT #URL-D-17-02046

**IMPACT OF ALLERGY AND RESISTANCE ON ANTIBIOTIC SELECTION FOR
RECURRENT URINARY TRACT INFECTIONS IN OLDER WOMEN**

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Key Words: recurrent urinary tract infection; women; antibiotic therapy; antibiotic resistance; antibiotic allergy

Response to Comments:

We appreciate the pertinent comments of this reviewer. Our database includes a unique subset of women with recurrent UTIs who have failed management by primary care providers and are subsequently referred to a urology practice. To our knowledge, this is the largest contemporary database reported detailing patient allergies and resistance along with antibiotic use and in a cohort in which greater than 50% had RUTI for 5 years or more.

Drug allergies are commonly overstated by patients.¹ However, when faced with a list of allergies, many practitioners do not have the resources available to them to provide referral to an allergist. Additionally, patients are often unwilling to comply faced with time-consuming doctor visits and testing. At our institution we commonly utilize drug provocation, which allows us to help recover antibiotic treatment options for women with RUTI.

Quinolones are indeed not first line empiric therapy as mentioned by several guidelines (Supplementary Table 3). Despite this, they are commonly utilized in this complicated subset of

patients who have been exposed to multiple antibiotic treatment options previously and failed. Therefore, it was a pertinent and valuable antibiotic to include in our analysis.

The management of RUTI is complex with no clear consensus from a variety of subspecialty guidelines (Supplementary Table 3). Patients with RUTI often have persistent and recurrent burdensome symptoms which are medically, financially and socially impactful. This may be due to loss of work productivity secondary to frequent voids, constant discomfort, days off for doctor visits and in some cases social isolation.² We do agree that chronic recurrent infection is likely due to inflammation and quiescent intracellular reservoirs of bacteria³ should be treated with goals of symptomatic relief and attempts at eradication of the source of the infection located in the bladder wall. Acute flare-ups with planktonic bacteria will respond to antibiotic treatment but bacteria embedded in the bladder wall will not. In that sense, we fully agree with the reviewer that only a bladder wall directed therapy is indicated. We have therefore managed women with RUTI and trigonitis with cystoscopy and fulguration of trigonitis, and shown successful eradication of trigonitis with long-term follow-up.⁴ This approach has been particularly useful in our small subset of patients with significant multidrug resistant organisms requiring IV therapy for RUTI management.

References:

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3. Anderson GG, Martin SM and Hultgren SJ: Host subversion by formation of intracellular bacterial communities in the urinary tract. *Microbes Infect.* 2004; **6**: 1094–1101.
4. Hussain SA, Alhalabi F and Zimmern PE: Long-term efficacy of fulguration of trigonitis for recurrent urinary tract infections in women. *Urol. Sci.* 2015; **26**: 197–201.