RECURRENT URINARY TRACT INFECTIONS DUE TO BACTERIAL PERSISTENCE OR REINFECTION IN WOMEN: DOES THIS FACTOR IMPACT UPPER TRACT IMAGING FINDINGS? A QUALITY IMPROVEMENT PROJECT.

by

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DISSERTATION

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ABSTRACT
RECURRENT URINARY TRACT INFECTIONS DUE TO BACTERIAL PERSISTENCE OR REINFECTION IN WOMEN: DOES THIS FACTOR IMPACT UPPER TRACT IMAGING FINDINGS?

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Background: It is recommended that women with recurrent urinary tract infections (RUTIs) due to bacterial persistence (same strain) undergo upper urinary tract imaging to evaluate for sources of their infection.

Objective: To compare the rate of upper tract imaging abnormalities between RUTIs due to bacterial persistence or reinfection.

Methods: Following IRB approval, a prospectively maintained database of women with documented RUTIs (≥ 3 UTI/year) and trigonitis was reviewed for demographic data, urine culture findings, and radiology-interpreted upper tract imaging study (renal ultrasound (US), CT scan, IVP) findings. Patients with irretrievable images, absent or incomplete urine culture results for review, no imaging study performed, an obvious source for RUTI, or history of pyelonephritis were excluded.

Results: From 2006 to 2014, 116 of 289 women with symptomatic RUTIs met inclusion criteria. Mean age was 65.0±14.4 with 95% being Caucasian and 81% post-menopausal. Nearly one-third were sexually active and none has prolapse >stage 2. Forty-one percent (48/116) had persistent and 59% (68/116) had reinfection RUTI. Imaging studies included US (52), CT (26), US and CT (31), and IVP with US/CT (7). Of total imaging findings (N=58 in 55 women), 57/58 (98%) were noncontributory. One case (0.9%) of mild hydronephrosis was noted in the persistent RUTI group but not related to any clinical parameters. *Escherichia coli* was the dominant bacteria in both persistent (71%) and reinfection (47%) RUTI in most recently reported urine culture.

Conclusion: This study reaffirms that upper tract imaging is not indicated for bacterial reinfection RUTI. However, the same conclusion can be extended to RUTI secondary to bacterial persistence, thus questioning the routine practice of upper tract studies in Caucasian post-menopausal women with RUTI and trigonitis.

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CHAPTER 1

PLAN

Background

Traditionally, the first step in the management of recurrent urinary tract infections (RUTIs) is to determine whether the etiology of the infection is bacterial persistence (same strain) or reinfection (different strain), as it greatly influences the urologic work-up of the patient. As stated in the 11th edition Campbell-Walsh Urology, bacterial persistence refers to RUTI caused by the "reemergence of bacteria from a site within the urinary tract (same bacteria)" and "infections that occur at close intervals" whereas bacterial reinfection is caused by "new infections from bacteria outside the urinary tract" occurring at "varying and sometimes long intervals."[1] The reason for differentiating between bacterial persistence and reinfection is also stated in the 2012 Campbell-Walsh Urology; "Although adult patients with bacterial persistence are relatively uncommon, their identification is important because they represent the only surgically curable cause of recurrent UTIs. A systematic radiologic and endoscopic evaluation of the urinary tract is mandatory."[1] Radiologic evaluation includes CT, cystoscopy, kidney and bladder ultrasound, and retrograde urography.[1] Likewise, the 2013 Smith & Tanagho General Urology textbook states that "When bacterial persistence is the suspected cause, radiologic imaging is indicated… In patients who have frequent, recurrent UTI, bacterial localization studies and more extensive radiologic evaluation (such as retrograde pyelograms) are warranted." Recommended tests include US of the genitourinary tract, and CT, IVP, and cystoscopy for a more detailed assessment.[2] In contrast, when

reinfection is the cause of the RUTI, radiologic evaluation of the upper tracts is not indicated.[2, 3] Important correctable upper tract findings include "infection stones, unilateral infected atrophic kidneys, ureteral duplication, ectopic ureter, foreign body, unilateral medullary sponge kidney, infected communicating cysts of renal calyces, and papillary necrosis".[1]

As part of a quality improvement project, we discussed the current guidelines with the stakeholders – Dr. Zimmern, the FPMRS fellow, and the database curator. After discussion with the stakeholders, they revealed concerns that the guidelines may not be valid in their population, since in their clinical experience they did not remember uncovering upper tract pathology in a patient with bacterial persistence. To further investigate the concerns of our stakeholders, we reviewed a large cohort of women with RUTIs due to bacterial persistence or reinfection to determine how often upper tract imaging was performed at our institution, and if correctable upper tract pathology was uncovered, and what predisposing factors, if any, were present.

Project Charter

The plan started with drafting the charter for this project. Roles were defined after identifying the project's primary stakeholders.

Next, we drafted the project description. The project alignment with UTSW hinged on the hospital's dedication to evidence-based medical practices to give patient's the gold

standard of medical care, while keeping patient's costs to a minimum, and considering the risk-to-benefit ratio of interventions. As part of our aim statement, we wanted to re-evaluate the validity of these guidelines in our population. The importance of this project was threefold: one, it would demonstrate if this guideline should be followed at UTSW; two, it may decrease overall spending on imaging; and three, it could potentially decrease the amount of contrast and radiation these patients may receive.

The scope of the project was defined as women with uncomplicated recurrent urinary tract infections. Deliverables included: rates of patients with bacterial persistence and reinfection, findings in each group, collection of demographics and possible risk factors, and a literature review of current data. The deadline for data analysis was defined as December 2016. No costs were projected to be associated with the project. Risks of the project include missing imaging, missing urine cultures, and inadequate data to determine significance. Other constraints include IRB approval for a retrospective review.

A communication plan was also defined, albeit loosely. Dr. Feras Alhalabi curated the database, giving it to the project manager, Lauren Rego. Data collection and analysis were done with Rose Wu and Lauren Rego communicating with each other. Meetings with the statistician Alana Christie were scheduled, with Dr. Zimmern always present, and either Lauren Rego or Rose Wu present to show collected raw data. Write up of findings were initially completed by Lauren Rego, with ongoing extensive edits by Rose Wu and re-analysis of data by Rose Wu. Dr. Fish communicated with Lauren Rego on the design of the project,

and helped draft the project charter and helped implement QI tools.

Literature Review

PubMed was queried about recurrent urinary tract infections in women and radiological findings. The initial search resulted in 1,013 results from 1980 to 2015, out of which only four had studies on upper tract findings in patients with RUTIs. The results of these studies are shown in Table 1. These were all older retrospective studies, with small patient populations, but did demonstrate women with RUTIs undergoing upper tract imaging studies have a low yield of correctable etiologies for their RUTIs (Table 1).

Cause and Effect Analysis

After the literature review, a brainstorming session was held with the stakeholders to determine why the guideline is implemented today, and what factors more specific to our institution contribute to scanning the upper tracts. These factors were sorted into four categories: the complexity of the patient population, our tertiary care referral pattern, the evidence behind the guideline, and provider bias. The results from this brainstorming session were organized into a cause and effect diagram shown in Figure 1.

After completion of the cause and effect diagram, it became apparent that we needed to intervene on the evidence arm. After discussion with the stakeholders, we planned to study our population, making sure to gather a cohort that was larger than previous studies.

CHAPTER 2

DO

Process Map (Current State)

First, we mapped out how the clinic processes women with RUTIs to understand how the process worked with multiple providers (Figure 2).

Methods

This is a retrospective study from an IRB–approved, prospectively maintained, database tracking the outcome of women with symptomatic RUTIs. Women with RUTI (3 or more uncomplicated UTIs in 12 months; a midstream urine bacterial count of at least 1 x 10^5 CFU/L should be considered a positive culture while the patient is symptomatic)[8] and trigonitis findings on office cystoscopy were included in this database.[9] Excluded were women with no upper tract imaging, reports but no images available for review, and/or no urine culture results available for review from their referral source. Also excluded were those with known etiology for RUTI (complicated RUTI) such as women performing clean intermittent catheterization (CIC), on an indwelling catheter, with a history of pyelonephritis, >stage 2 anterior compartment prolapse, or neurogenic bladder[10]. Children and pregnant women were excluded.

RUTI patients underwent an extensive evaluation including history, physical examination, urine culture, cystoscopy and ≥1 upper tract study. Collected demographic

data included race, BMI, gravidity, parity, prior urine culture results of infecting strains to distinguish persistence versus reinfection, diabetic status, immunosuppression status (corticosteroids, immunosuppressant medications, chemotherapy), menopausal status, sexual activity, degree of cystocele, history of pyelonephritis, and history of kidney stones. Data was acquired through an electronic medical record (EPIC) by a reviewer not involved with patient care. Imaging studies in EPIC were either from studies performed at our own institution or, when performed at an outside institution, fully loaded into EPIC, therefore amenable to review.

All findings during office flexible cystoscopy were documented with photographs recoverable for review in EPIC. All women in this cohort had trigonitis defined as chronic mucosal inflammation of the trigone (not pseudomembranous trigonitis or squamous metaplasia of the trigone) (Figure 3), and diagnosed by the same experienced urologist and/or his FPMRS-trained physician assistants.[11,12]

Upper tract imaging was obtained with renal ultrasound (US), CT urogram (CT), or intravenous pyelogram (IVP). Regarding key radiological findings, PubMed was queried for the search terms “urinary tract infections” and “classification or pathology or radiography or ultrasonography.” The search yielded 1,013 results from 2015 to 1980. Articles not in English, or about acute UTIs, or related to men, children, or pregnant women were excluded. Relevant textbooks and cited papers were also reviewed. Based on this literature review, a list of key radiological findings reported with RUTIs was prepared including: hydronephrosis,

ureteral duplication, renal lesions (tumors, cysts, diverticulum, uncharacterizable lesions), kidney stones, pyelonephritis, and perinephritic inflammation. Each imaging study with an abnormal finding was reviewed to confirm the official radiology report. Bacterial persistence and reinfection were analyzed based on bacterial strains and minimum interval time between 2 positive urine cultures.

Statistics

Descriptive statistics were calculated using means and standard deviations for continuous measures, and frequencies and percentages for categorical measures. Fisher's exact test was used to test for association between history of kidney stones and findings of kidney stones. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

CHAPTER 3

STUDY

From 2006 to 2014, 289 women with RUTI were prospectively entered into a database and selected for this upper tract evaluation study. One hundred and seventy-three women met our exclusion criteria (neurogenic bladder (8), CIC (5), indwelling catheter (2), no upper tract study retrievable (87), images not available for review (15), prior urine culture results not available for review (53), > stage 2 anterior compartment prolapsed (2), history of pyelonephritis (1)). The large number of not retrieved upper tract studies and urine culture results stemmed from our tertiary care referral pattern with many patients presenting with supporting evidence of negative imaging studies done elsewhere in the past, but no access to the films themselves so that they could not be reviewed as part of this study. Likewise, even when the patient knew her type of bacteria or the referral letter listed it, they were excluded from the study because the urine culture results could not be reviewed by us.

The final cohort included 116 patients, each of whom had one or more retrieved upper tract imaging study. Patients either underwent US alone (N=52), CT alone (N=26), US and CT (N=31), or IVP with US or CT (N=7). Demographic findings are presented in Table 2. Of the 116 patients, 48/116 (41.4%) were found to have persistent RUTI (same strain) and 68/116 (58.6%) were reinfection RUTIs (different strains). The two most common bacteria for both groups were *Escherichia coli* and *Enterococcus faecalis.* Specific bacterial strains found in each cohort were summarized in Table 3.

A final count of N=58 imaging findings were noted in 55/116 women, since a few patients had more than one finding on their imaging studies. Incidental findings (N=57) included 6 non-obstructive kidney stones, 44 lesions (37 cysts and 7 uncharacterizable (hypodense) renal lesions), and 7 partial ureteral duplications (Table 4). Two of 9 (22.2%) patients with kidney stone history had stones on imaging versus 4/107 (3.7%) of patients that did not have such history had stones on imaging ($p = 0.0685$). Stones ranged from "tiny/minimal" to 3mm. No renal scarring or staghorn calculi were identified. None of the small stones or partial ureteral duplication identified in this study was related to hydronephrosis.

Mild hydronephrosis was noted in 1/116 (0.9%) woman with persistent RUTI on US. This woman was evaluated for clinical risk factors of RUTIs, but no clinical parameters (BMI, gravida, parity, immunosuppression, kidney stones, degree of cystocele, infecting strain) was correlated with these upper tract findings. In addition, this woman also underwent a voiding cystourethrogram to exclude reflux, and that study was negative. Furthermore, the hydronephrosis was mild, thus no surgical intervention was deemed necessary.

Repeat imaging of the upper tracts was noted in 35 women (30.2%). These studies were ordered by various physicians over the span of the study. Of those 35 patients, 3 had multiple CT scans and 8 had both CT and US due to evolving medical problems (abdominal hernia, quadrant pain, tumors, or re-evaluation of RUTI). One patient had multiple US

scans for reasons ranging from re-evaluation of RUTI to new onset flank pain, over the course of years. For similar reasons, 9 patients underwent US followed by CT and 14 CT followed by US. Even when upper tract studies were repeated, or obtained with a different imaging technique, there was no change in the final abnormality findings related to RUTIs, i.e. CT did not detect additional findings not noted on ultrasound, and vice-versa. Therefore, CT scan was found equally sensitive than US in detecting upper tract abnormalities.

CHAPTER 4

ACT

The purpose of this study was to evaluate the merit of systematic upper tract imaging in non-neurogenic women with RUTI, a common referral in our tertiary care center. We found a very low rate (0.9%) of upper tract imaging positive findings (mild hydronephrosis and no perinephritic inflammation or pyelonephritis) in the persistence group, and none in the reinfection group. Imaging studies included US more so than CT scan or IVP. No demographic risk factor was identified to help select the best possible candidate for upper tract evaluation in women with RUTIs.

According to several trusted sources, upper tract imaging is recommended in the evaluation of women with RUTI and bacterial persistence.[2, 3] Our very low findings appear consistent with the limited literature information reported so far on the rate of upper tract abnormalities that could be causing RUTIs. In a review on urinary tract infections by Najar et al. in 2009, a statement was made that upper tract abnormalities in women after an acute UTI were "found in less than 5% of cases."[13] However, there was no reference to support that quote, and no reference specifically for RUTIs. [13] In addition, none of the other major textbooks referring to RUTIs mentioned the rate of upper tract findings.[2, 3] It is recognized that patients with RUTIs should undergo cystoscopy. RUTIs associated with certain clinical factors such as prior urinary tract surgery, hematuria, previous renal or bladder calculi,

obstructive symptoms, diabetes or immunosuppression, or unresolved UTI,[1] should undergo an upper tract evaluation.[10,14]

In our study, 98.3% of imaging findings were incidental, including 10.3% non-obstructing small size stones, 12.1% hypodense lesions, 12.1% partial duplication, and 63.8% renal cysts. Women with a history of renal stones and RUTI should be evaluated for stones, but none of the women in this study had obstructive kidney stones or staghorn stones. The single woman with positive upper tract findings (mild hydronephrosis) had persistent *Escherichia coli* infection, but no correlation was observed with presenting symptoms, examination findings, or UTI risk factors.

The strengths of this study include the 8 year span of patient collection and a relatively large database. Women included in this database were part of an ongoing prospective study on refractory RUTIs. They were different from women with acute urinary tract infections in that they all had documented trigonitis and RUTIs despite multiple rounds of antibiotic therapy, thus representing a more tenacious form of UTI for which one might have expected a possibly higher rate of upper tract abnormalities. All women in our study underwent office cystoscopy to search for an RUTI etiology and exclude malignancy.[14] Even in this chronic high-risk group, imaging the upper urinary tracts yielded extremely low positive findings in the persistence group and none in the reinfection group.

Since the nature of this study was retrospective, patients' investigations were not

uniform. Data was not available on all women, and the physician ordering radiologic evaluation came from a variety of departments including Internal Medicine, Family Practice, and Urology. Also, some studies were not retrievable but their results, although unknown to us, might have influenced the final detection rate of upper tract abnormalities. Therefore, one could argue that this population of women already evaluated for RUTI was skewed, since upper tract anomalies might have been already identified and corrected. This valid criticism could have limited the relevance of our study. However, based on patient history, even in those in whom the imaging studies could not be reviewed, there was no report of prior upper tract pathology and/or corrective upper tract intervention, thus eliminating this possible bias. In regards to generalizability, a clear limitation is that our findings predominantly apply to Caucasian and post-menopausal women. Regrettably, because the yield of upper tract imaging findings was so low in our study, we were unable to characterize clinical factors to select an ideal RUTI candidate for upper tract imaging investigations. Also, one could argue that the optimal timing to detect upper tract changes would be in the early phase of the infection. However, all studies so far, including ours, reported on imaging findings obtained later on.

Finally, one could contend that the presence of trigonitis is a nidus for ascending upper tract infections, acting as a chronic bacterial reservoir explaining bacterial persistence in postmenopausal women otherwise not sexually active. Eradication of trigonitis has been associated with a significant reduction in RUTIs.[11] Therefore, our cohort could, in theory, have more upper tract pathology than a group of women with RUTIs with negative

cystoscopic findings; but this was not the case in this series. However, the counterargument could be made that RUTIs in the presence of a normal bladder on cystoscopy could originate from an undiscovered upper tract pathology, thus justifying such a routine imaging investigation. Consequently, a limitation of this study is the lack of a cohort of women with negative office cystoscopy to compare with our group exhibiting trigonitis.

In addition, the one-provider analysis – and thus process map – do not show what happens when women with RUTIs are referred to other FPMRS clinicians, or if they are referred to the general urologists.

The average cost of these imaging modalities is high, much more for CT scan than renal ultrasound, not including professional costs. Given our very low percentage of positive upper urinary tract findings possibly linked with RUTI, and the cost of many of these imaging techniques, the recommendation to image the upper urinary tracts in many women with RUTIs secondary to persistence or reinfection may need to be reconsidered.

Act

Publication

We published our findings in the Journal of Urology, the premier journal for urology.[15] The publication sparked a response from the editor, and we presented our data the American Urological Association. Adding our data to the body of literature will hopefully continue to spur further investigation into these guidelines. Additional strong data is needed before the

guidelines will be changed, such as a randomized controlled trial.

Intervention and Scalability

After the publication, the guidelines remained in place. Even given that in our retrospective study we found a very low rate of upper tract findings for the patient population at UTSW, the provider must still adhere to guidelines. In addition, this means that the original process map from before the study will remain unchanged. The question of whether this process map is scalable to other providers remains to be determined. The process map may not be scalable due to the one-physician process.

Conclusion

As part of a quality improvement project, this study indicates that routine upper urinary tract imaging has a very low yield (0.9%) for upper tract anomalies related to RUTIs in predominantly post-menopausal Caucasian women with trigonitis whether in the bacterial persistence or reinfection groups. Therefore, the current recommendation to study the upper tracts of women with RUTIs may have to be reconsidered, especially given that women with surgically correctable causes were not found in this study and the imaging cost may be substantial.

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Table 1:
Literature Review: Women with RUTIs with Correctable Pathology

Author	Year	N =	Age	US	IVP	VCUG
Engel G, et al.[4]	1980	153	40.3 (15.7)*		0%	
Fairchild TN, et al.[5]	1982	78	19-35**		[Δ]	6.4% ***
Aslaksen A, et al.[6]	1990	124	44****	5.6%	5.6%[ΔΔ]	
Haarst EP[7]	2001	100	18-40**	1%	0%	

* Mean age (Standard Deviation)
**Age range
***IVP and VCUG together
**** Median age
[Δ]ectopic duplicated ureter, medullary sponge kidney with stones, vesicoureteral reflux, ureterocele, pyelonephritic kidney
[ΔΔ] pyelonephritic changes, hydronephrosis and calculi (most ≥5mm)

Table 2:
Patient Demographics (N = 116)

	N/Total (%)
Age (avg. ± std. dev.)	65.0 ± 14.4
BMI (avg. ± std. dev.)	26.5 ± 6.5
Race	
Caucasian	110/116 (94.8)
Other	6/116 (5.2)
Gravidity	
0	10/86 (11.6)
1	13/86 (15.1)
2	28/86 (32.6)
3	20/86 (23.3)
4	9/86 (10.5)
5	2/86 (2.3)
6	4/86 (28.2)
Parity	
0	12/88 (13.6)
1	16/88 (18.2)
2	30/88 (34.1)
3	22/88 (25)
4	4/88 (4.5)
5	4/88 (4.5)
Diabetes	8/116 (6.9)
Immunosuppression	6/116 (5.2)
Post-Menopausal	94/116 (81)
Sexually Active	33/116 (28.4)
History of Kidney Stones	9/116 (7.8)
Anterior Compartment Prolapse	
Stage 0	62/103 (60.2)
Stage 1	32/103 (31.1)
Stage 2	9/103 (8.7)
Current Chemotherapy	2/116 (1.7)

Table 3:
Distribution of Bacterial Strains In RUTI Patients (N = 116)

	N/Total (%)
Persistent RUTI	48/116 (41.4)
Reinfection RUTI	68/116 (58.6)
Persistent RUTI	**N=48**
Escherichia coli	34/48 (70.8)
Enterococcus faecalis	8/48 (16.7)
Klebsiella pneumoniae	4/48 (8.3)
Staphylococcus epidermidis	2/48 (4.2)
Reinfection RUTI*	**N=68**
Escherichia coli	32/68 (47.1)
Enterococcus faecalis	12/68 (17.6)
Klebsiella pneumoniae	9/68 (13.2)
Staphylococcus epidermidis	4/68 (5.9)
Streptococcus agalactiae	3/68 (4.4)
Proteus mirabilis	2/68 (2.9)
Citrobacter freundii	2/68 (2.9)
Staphylococcus aureus	1/68 (1.5)
Staphylococcus saprophyticus	1/68 (1.5)
Enterobacter cloacae	1/68 (1.5)
Pseudomonas fluorescens	1/68 (1.5)

Table 4:
Imaging findings in women with bacterial persistent or reinfection RUTI (N=116)

		Total	**Persistence**	**Reinfection**	***p***
Upper Tract Imaging Studies (N=116)	US Only	52	21	31	0.0539
	CT Only	26	6	20	
	US + CT	31	16	15	
	IVP + US/CT	7	5	2	
Abnormal Findings (N=58)*	Partial Ureteral Duplication	7	3	4	1.0000
	Non-obstructing renal stone	6	1	5	0.3983
	Renal cyst	37	20	17	0.0702
	Hypodense small renal lesion	7	4	3	0.4457
	Mild hydronephrosis	1	1	0	0.4138

*Fifty-eight abnormal imaging findings in 55 women

LIST OF FIGURES

Figures 1: Cause and effect diagram of potential causes of overimaging the upper urinary tract in women with RUTIs.

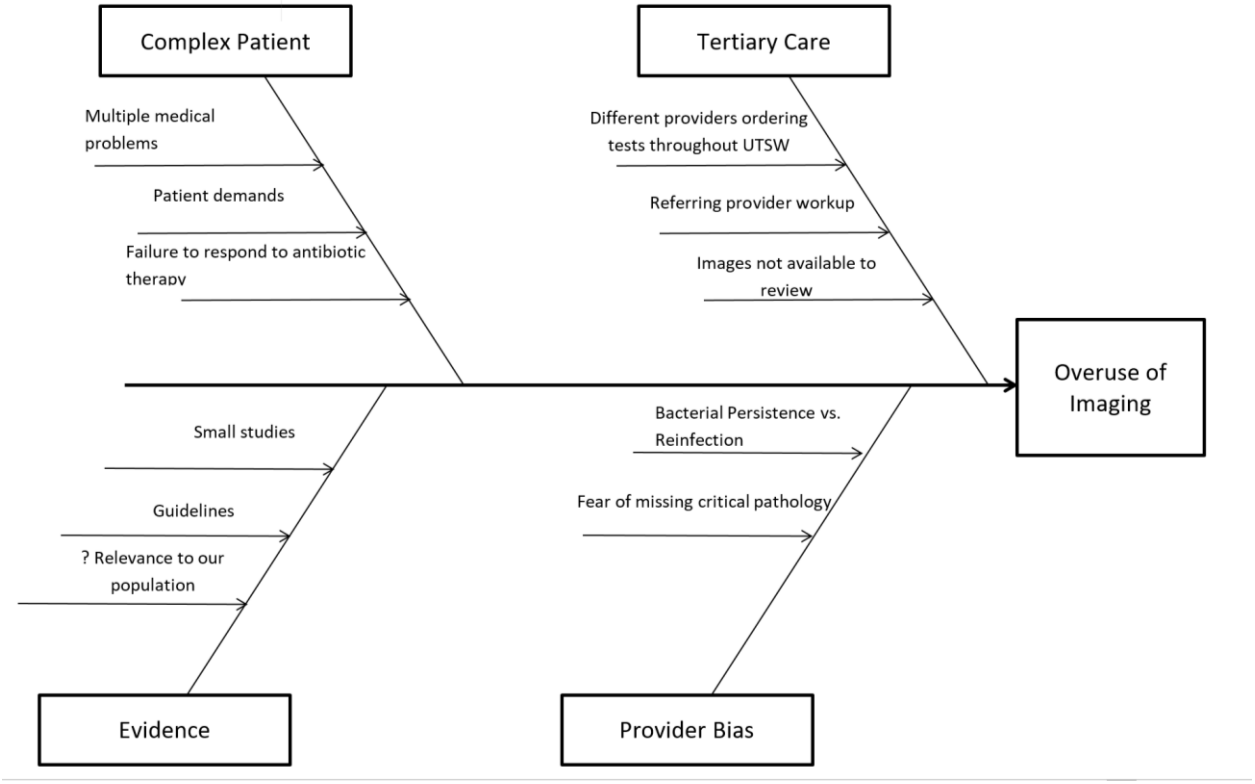


Figure 2: Process map of workup of women referred to Dr. Zimmern's clinic for RUTIs

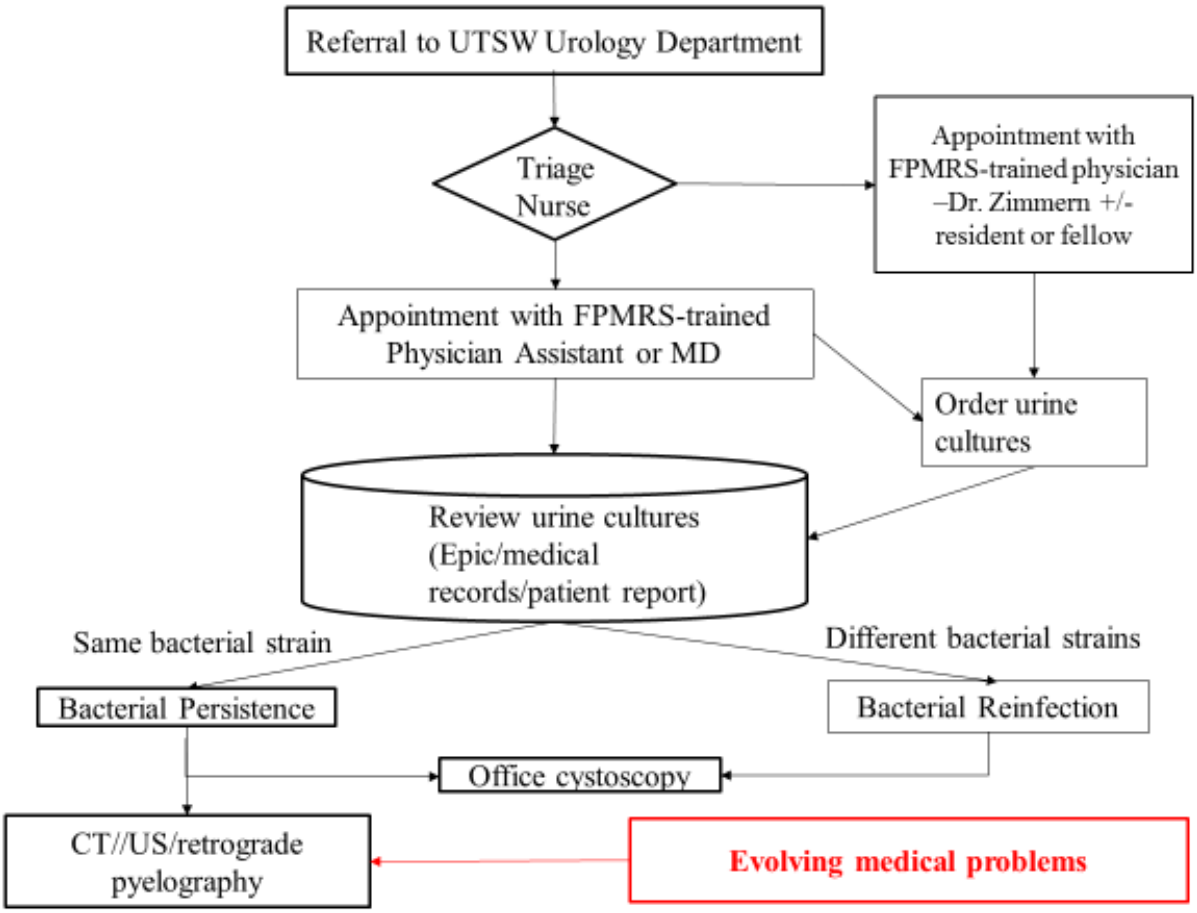
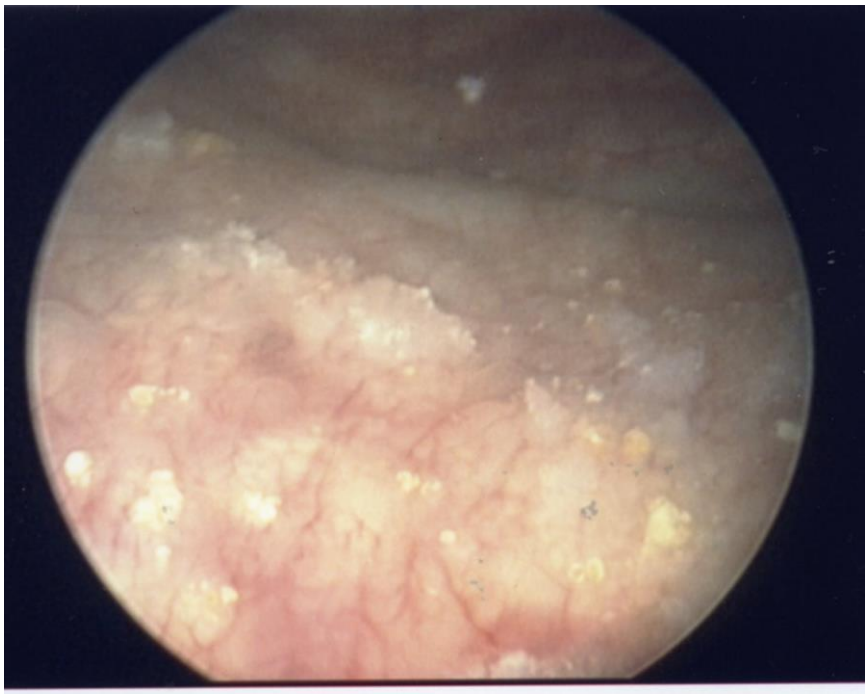
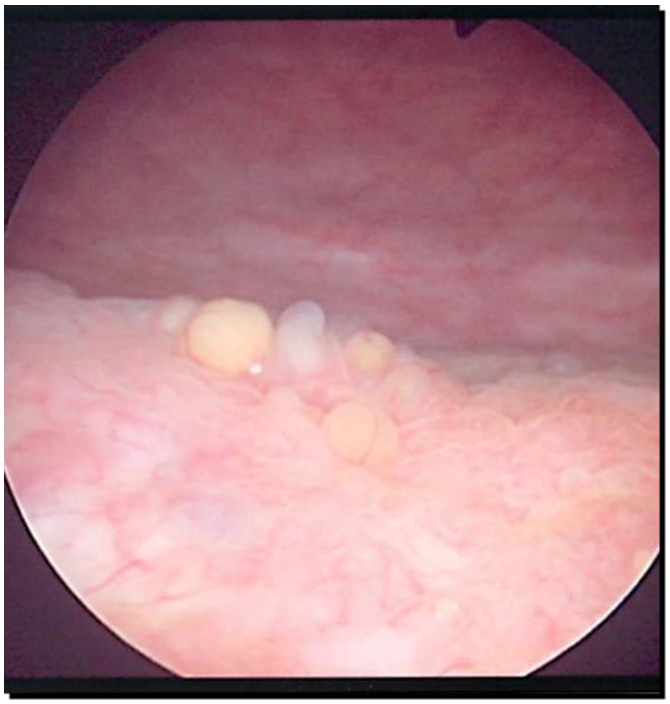


Figure 3: Endoscopic examples of trigonitis: (A) chronic areas of encrustations; (B) large yellow, pus-filled, pockets emerging on a background of bullous cystitis





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VITAE

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