Inflammation in Women with Urgency Urinary Incontinence Treated with Anticholinergics

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I. Specific Aims

Specific Aim 1: To assess inflammatory markers in urine and serum before and after a 6-week treatment course with anticholinergics.

Specific Aim 2: To determine the role of urinary microbiome in relation to inflammation before and after a 6-week treatment course with anticholinergics.

II. Background & Significance

Urinary incontinence (UI) is a very common condition affecting women of all ages. UI is an emotionally, socially, physically and economically burdensome condition (1). It has a significant impact on quality of life (QOL), where urinary incontinence has been shown to be associated with embarrassment, anxiety, and depression. Total costs of UI (direct and indirect) are about $11 billion/a year (2).

The influence of the human microbiota on normal health and disease conditions is increasingly appreciated in a variety of medical fields (3). The hypothesis of “sterile” bladder has recently been disputed (4), leading to a series of investigations about the role of urinary microbiota in urinary incontinence. Stress urinary incontinence does not appear to be associated with urinary microbiota (5), while urgency urinary incontinence (UUI) is highly related to microbial status and diversity (4,5). The role of inflammation in relation to urinary microbiome is understudied among women treated for UUI. An important emerging question is whether the inflammatory milieu and urinary microbiota interact and vary over time, and in particular, in response to UI treatment.

Data from the Anticholinergic Versus Botulinum A Comparison (ABC) Trial showed that women with sequence-positive urine samples (DNA positive) responded better to treatment (anticholinergics or botulinum toxin A) and had decreased number of UUI episodes (6). Furthermore, those women had less urinary tract infections (6). A study solely devoted to analyzing the role of urinary microbiome in the treatment of UUI with solifenacin (anticholinergic) showed changes in microbial abundance after 12-week treatment (7). Clinically, many women with UUI fail pharmacologic treatment options with anticholinergics.

We hypothesize that an increased inflammatory response due to an altered urinary microbiome at baseline predisposes women to a higher rate of failure of UUI treatment with anticholinergic medications. The objective of this pilot study is to better understand the urinary microbiome and associated inflammatory markers in blood and urine in women with UUI, and whether they vary over time secondary to anticholinergic treatment. To address this goal, we plan to enroll 20 women with UUI presenting to our Urogynecology Clinic.

References

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III. Research Design and Methods

Study design, population, and inclusion/exclusion criteria

This study is designed as a prospective pilot research of women presenting to our Urogynecology Clinic in our Boston or Foxborough locations with UUI symptoms. The inclusion criteria are women who have a diagnosis of UUI and are willing to participate in the study and provide their blood and urine for research purposes. The exclusion criteria are: lack of consent, neurological disease such as Parkinson's or Multiple Sclerosis, known immunological deficiencies, history of UTI in the last 3 months, history of taking anticholinergics within the last month, history of antibiotics use in the last month, history of sexually transmitted diseases.

We plan to enroll 20 women who are offered treatment with a standard of care anticholinergic medication for 6 weeks. The patient's provider will explain the study to eligible patients and consent will be obtained by the research assistant. Once consent is obtained, a catheterized urine sample will be collected from the patient as well as a blood draw by the phlebotomist at the Center of Clinical Investigation at Brigham and Women's Hospital or at the phlebotomy lab at The Brigham Health and Brigham and Women's/Mass General Health Care Centers in Foxborough. Participants will be asked to fill the UDI-6 questionnaire and they will be given a two-day diary to complete at home before they start the anticholinergic medication. They will be then asked to follow up 6 weeks later. Prior to the 6-week follow-up visit, participants will fill another 2-day voiding diary and complete the UDI-6 questionnaire. At the 6-week visit, a repeat catheterized urine sample will be taken for microbiome and inflammatory markers analysis but no blood draw. The urine will be assessed by enhanced urine cultures and DNA sequencing for urinary microbiome at baseline and again at 6 weeks. Inflammatory mediators will also be tested in urine and blood. The microbiome analysis and bioinformatic analysis will be performed by two experienced Harvard Research Core Labs. Inflammatory mediators will be tested by a third Research Core Lab at Boston University. Baseline urinary symptoms at enrollment and variation of symptoms after 6 weeks of anticholinergic treatment will be assessed using a two-day bladder diary and a validated UI questionnaire (UDI-6).

IV. Study procedures

a. **Visit of enrollment:** Participants presenting with UUI diagnosis will complete the informed consent document and a baseline UDI-6 questionnaire. (Appendix A). This survey consists of 6 questions to assess the nature and severity of urinary incontinence symptoms at baseline. In addition, participants will be asked to provide urine sample for microbiome and immune markers and blood samples solely for immune markers. Participants will be given 2-day bladder diaries to fill out at home and before starting anticholinergic treatment.

b. **Randomization/treatment allocation*:*** Randomization will not be performed. All patients will receive treatment with anticholinergics for a duration of 6 weeks.

c. **Follow up visit after 6 weeks:** Participants will complete another 2-day voiding diary prior to their visit and they will be asked to bring the diaries to their visit. They will also complete the UDI-6 questionnaire to assess changes in urinary symptoms after 6-weeks of anticholinergic treatment. Patients will be evaluated for drug effectiveness by the treating urogynecologist. Urine will be taken for repeated analysis of microbiome and immune markers.

V. Outcome measures

a. Primary outcome: To assess if the urinary microbiome is associated with inflammatory and immune changes in women with UUI.

b. Secondary outcomes: To assess the effectiveness of anticholinergic treatment in relation to the urinary microbiome and immune status over a 6-week course, and to investigate if the interaction of urinary microbiome with host through immunologic markers may alter responsiveness to standard of care treatment with anticholinergics.

VI: Statistical Considerations

Descriptive statistics will be employed to describe and compare data using parametric statistical tests for normally distributed data and non-parametric tests for non-normally distributed data. We will then specifically evaluate the role of microbiome on UUI in our subgroups. Wilcoxon test and Mann Whitney test will be applied to estimate the possible differences. The correlation between microbiome and inflammatory markers before and after treatment will be assessed by the Spearman's rank correlation. Harvard Catalyst Statisticians will be consulted for statistical analysis.

VII. Data Collection and Transmission

Additional data to be abstracted from the medical records include: age, race, BMI, parity, smoking status, menopausal status, comorbidities, present medications (including hormone replacement), use of contraceptive medications, use of vaginal estrogen, previous hysterectomy surgery, previous removal of ovary(ies), last menstrual period date and the use of tampons, previous surgeries for urinary incontinence, duration and type of UI symptoms, presence of prolapse.

All study procedures will be conducted in a manner respectful to maintaining patient confidentiality. All patient data will be kept confidential and appropriate procedures will be implemented to assure that patient confidentiality is maintained, including the following: files will

be maintained on password protected computers. The data will be accessible only to the study personnel. Any publication, presentations, or reports from this research study will maintain the anonymity of study subjects.

VIII. Human Subject Research and Ethical Concerns

Signed consent in English will be obtained from each participant at the time of enrollment. In the event that a non English-speaking patient meets inclusion criteria and is willing to participate, a short form consent document will be administered in the presence of a medical interpreter obtained through Interpreter Services as per Partners IRB guidelines. The objectives of the study and the data collection procedures will be explained to every prospective participant before enrollment. An IRB-approved consent document will be used. Consent for participants will include the following rights:

- To either withdraw or refuse participation without prejudice at any time during the study;
- To voluntarily participate in the research;
- To receive new information about the study as it becomes available;
- To understand the procedures, risks, and benefits;
- To maintain confidentiality of personal medical information.

Protection Against Risk: The foreseeable risks include those related to the study procedures which include blood taking that may be related to pain, discomfort and bruising, however these are short-lasting and transient. Obtaining a urine sample using a catheter may lead to minimal pain or discomfort.

Confidentiality: Our research staff will take every precaution to protect the confidentiality of the collected data. All personnel who will have access to collected data have completed the Program for Ethics Education in Research training with the appropriate HIPAA certification. After obtaining initial informed consent, a numerical code will be assigned to each participant. This number will correspond to the participant's name in a separate file called a "key." The key will be kept in a locked filing cabinet in the principal investigator's office. Only the study investigators and research coordinator will have access to this cabinet. Completed data forms and paper questionnaires will be placed in a separate locked file cabinet, and only authorized staff members will have access to the data. Only de-identified data will be entered into a computerized database that is stored on computers which are safeguarded by passwords known only to authorized personnel. The data that are collected will be used strictly for the purposes of the research in question. Any printout information will be destroyed once the project is completed and the manuscript is published.

IX. Timing of Study and Recruitment:

This is a pilot study that we expect will be completed within 6-9 months. Approval of IRB application is anticipated to occur within 6 weeks. We expect to enroll 20 patients within 3 months of study initiation. This will be followed by another 6 weeks for patient follow-up, data collection and entry. All urinary and blood microbiome and inflammatory analysis, including the bio-informatics, will be promptly performed by the three Research Core Labs. Final analysis, submission of findings to national meetings, and preparation of manuscript will be completed in another 3 months.

X. Appendices

Appendix A: UDI-6 questionnaire

The following symptoms have been described by women who experience accidental urine loss. Please indicate which symptoms you are now experiencing and how bothersome they are for you. Be sure to answer all items.

A. Do you experience frequent urination?

☐ Yes ☐ No (skip to B)

↓

If 'yes', how much does it bother you?

Not at all	slightly	moderately	greatly
☐	☐	☐	☐

B. Do you experience urine leakage related to a feeling of urgency?

☐ Yes ☐ No (skip to C)

↓

If 'yes', how much does it bother you?

Not at all	slightly	moderately	greatly
☐	☐	☐	☐

C. Do you experience urine leakage related to physical activity, coughing or sneezing?

☐ Yes ☐ No (skip to D)

↓

If 'yes', how much does it bother you?

Not at all	slightly	moderately	greatly
☐	☐	☐	☐

D. Do you experience small amounts of urine leakage (that is, drops)?

☐ Yes ☐ No (skip to E)

↓

If 'yes', how much does it bother you?

Not at all	slightly	moderately	greatly
☐	☐	☐	☐

E. Do you experience difficulty emptying your bladder?

☐ Yes ☐ No (skip to F)

↓

If 'yes', how much does it bother you?

Not at all	slightly	moderately	greatly
☐	☐	☐	☐

F. Do you experience pain or discomfort in the lower abdominal or genital area?

☐ Yes ☐ No

↓

If 'yes', how much does it bother you?

Not at all	slightly	moderately	greatly
☐	☐	☐	☐

Appendix B:

DAILY VOIDING DIARY

NAME_____ Birth Date_____ Date_____

Time of Day	Type & Amount of Fluid Intake	Amount Voided (Ounces or cc)	Amount of Leakage (small, medium, or large)	Was Urge Present?	Activity With Leakage
12:00a					
1:00					
2:00					
3:00					
4:00					
5:00					
6:00					
7:00					
8:00					
9:00					
10:00					
11:00					
12:00p					
1:00					
2:00					
3:00					
4:00					
5:00					
6:00					
7:00					
8:00					
9:00					
10:00					
11:00					

Comment: _____

Number of pads used in 24 hours: _____

HOW TO KEEP YOUR BLADDER DIARY?

The main purpose of a bladder diary is to document how your bladder works. A diary can give us an excellent picture of your bladder functions, habits and patterns. The diary is used as an evaluation tool. Please complete the bladder diary for 3 days and bring it with you to your appointment.

In the beginning, continue to go about your daily life as normal. You are making a written record of your normal bladder patterns so please avoid making any changes in your bladder routines. Your diary will be much more accurate if you fill it out as you go through the day. It can be very difficult to remember at the end of the day exactly what happened in the morning. The diary plays an important part in your health care provider's ability to understand your problem and should not be taken lightly.

Also, if possible, remember to change your pad or clothing whenever you feel yourself leaking or notice that you are damp. A dry pad or pair of underwear will increase your awareness of problems and improve the accuracy of your record.

INSTRUCTIONS

Column 1 - Type & Amount of Fluid Intake & Food Intake*:*
Record the type and amount of fluid you drank, and food you ate.

Note the hour you went to sleep and when you woke up for the day.

Column 2 - Amount Voided (Urinated):

Place the measured amount of urine in the box with the appropriate time interval each time you urinate during the day. You need to fill in ounces or cc (ml) (30 ml / cc equals about one ounce). Use a urine collection "hat" or measuring cup for accurate amounts. Urine is sterile so using a baking measuring cup may seem gross but it is OK – other ways to measure include counting 1 Mississippi, 2 Mississippi, 3 Mississippi. If the stream is steady, for each "Mississippi" you have urinated 1 ounce. Don't count fast.

Column 3 - Amount of Leakage:

SMALL = drop or two of urine in your underwear or pad
MEDIUM = wet pad but not outside
LARGE = wet pad and outerwear or leaking down the legs or onto the floor

Column 4 - Activity with Leakage & Was Urge Present:

Describe the activity associated with the leakage i.e. coughing, sneezing, bending, lifting, running, jumping, hearing running water, going outside, having a strong urge.
Describe the urge sensation you had to go as:

MILD= first sensation or desire to go.
MODERATE = stronger sensation or desire to go.
STRONG = a very strong sensation or desire to go or get to toilet, move aside!