**Student: Laura Barnes**
**Section leader: Beth Cohen**
**Participate in critique: No**

# Impact of Antibiotics and Local Breast Microbiome on Implant Infection Rate After Breast Reconstruction

**Investigators**
Principle Investigator: Merisa Piper, MD
Co-Investigator: Laura Barnes, MD

**Abstract**
Breast implant infection is a substantial cause of morbidity in patients who undergo mastectomy with implant-based reconstruction, with reported infection rates between 5.8-28%. Prior studies have demonstrated static differences in the breast microbiome in women with breast cancer compared to healthy controls. The local breast microbiome has never been investigated with respect to implant infection, and the use of post-operative antibiotics in this population, while standard practice many surgeons, is not evidence-based. We propose a pilot study primarily testing the feasibility of our novel technique in sampling the breast microbiome over time, secondarily assessing the impact of post-operative antibiotics and the local breast microbiome on the development of implant infection in women undergoing mastectomy with implant-based reconstruction. It is designed as a prospective, randomized-control study. We will recruit 40 patients to the pilot study – 20 to the treatment group and 20 to the control group. The treatment group will receive post-operative antibiotics while the control group will not receive post-operative antibiotics. All patients will have their breast microbiome sampled five times: one intra-operative tissue sample followed by four weekly peri-expander aspirate samples. The primary outcome under investigation is feasibility of our technique, with a secondary outcome of implant infection within 90 days of surgery.

**Research Questions**
*Primary question:* In women with breast cancer undergoing mastectomy with implant-based breast reconstruction, does receipt of post-operative antibiotics have an impact on the development of severe implant infection (requiring implant removal)?

*Secondary question:* In women with breast cancer undergoing mastectomy with implant-based breast reconstruction, does the local breast microbiome impact the development of implant infection, and do antibiotics have an impact on the breast microbiome and the subsequent development of infection in this population?

**Specific Aims**
1. To determine the feasibility of breast microbiome sampling using the techniques we outline below.
2. To determine the effects of post-operative antibiotics on the development of post-operative infection and on the breast microbiome after mastectomy with implant-based reconstruction.

3. To define the differences in the breast microbiome between patients undergoing mastectomy with implant-based reconstruction who develop post-operative implant infection and those who do not.

**Significance**

Postoperative infections in breast cancer patients have significant downstream consequences, including reconstruction delay and failure. In the United States, one in eight women will be diagnosed with breast cancer in her lifetime.[1] Approximately 50% of these women will undergo some form of breast reconstruction following mastectomy, with the most common method by far (>70%) being implant-based reconstruction.[1,2] Post-operative infections are a significant cause of morbidity in this operation, with reported infection rates ranging from 5.8% to 28%.[3,4] These rates are considerably higher than the 0.1% to 1.5% infection rates reported in cosmetic breast augmentation.[13]

Infections in the breast cancer population can have serious consequences, not only by delaying definitive reconstruction but also by delaying cancer-related treatments, including chemotherapy and radiation.[16] Infections may lead to reconstructive failure requiring readmissions and reoperations, and the use of broad-spectrum antibiotics to treat infections can lead to antibiotic resistance patterns.[17]

Whether the breast microbiome—which differs between patients with breast cancer and healthy controls—plays a role in postoperative infection is an intriguing but understudied question. Epidemiologic studies suggest that the human microbiome contributes to 15-20% of worldwide malignancies.[18,19] While there are established, non-infectious risk factors for the development of breast cancer, at least 70% of cases occur in women with no clear cause.[20] Prior studies have found that diets high in fat and low in fiber have been associated with changes in the gut microbiome which are postulated to lead to an increased risk of breast cancer development.[11,12] Alcohol use, which is associated with breast cancer development, has also been associated with quantitative and qualitative changes in the gut microbiome and with increased risk of breast cancer.[11,12] Additionally, breast tissue, previously thought to be sterile, has been found to harbor its own microbiome.[5-10] A current hypothesis is that bacteria of the breast microbiome are of either ductal origin (entering ducts through lactation, sexual oral contact, or from the adjacent skin microbiota), or from enteric transposition.[21,22] The breast microbiome in patients with breast cancer has been shown to differ significantly in diversity measures and in abundance of certain microbes when compared to healthy controls.[5-10] Recent studies suggest the microbiome can affect rates of infection and post-operative complications in other surgical fields.[14,15] Breast cancer patients may harbor abnormal breast and gut microbiomes.[5-10] These microbiomes can potentially be manipulated by antibiotics. However, this has not been studied in the setting of mastectomy with implant-based reconstruction. All prior studies that evaluated the breast microbiome did so with only one tissue sample from the operating room and did not observe the microbiome over time. Our overall goal is to understand the role of the breast microbiome in the development of implant-based post-mastectomy complications, and how antibiotics impact the microbiome and overall outcomes.

It is possible that the routine use of antibiotics is counterproductive – a contributing cause to implant loss and infection may be the generation of a biofilm, which may be caused by specific species in the microbiome fostered by antibiotics with simultaneous suppression of other species.[23,24] We propose to explore the influence of the microbiome on post-operative infections by understanding the influence of the use of antibiotics on the peri-expander serum/aspirates.

The proposed work is significant because it has the potential to increase our understanding of a poorly understood phenomenon – post-mastectomy implant infection. We propose to collect preliminary data to understand how antibiotics impact the breast microbiome in this patient population. Our central hypothesis is that the breast microbiome is unique in patients who develop infections after mastectomy with implant-based reconstruction. The rationale for the proposed research is that once it is known how certain variances in this microbiome increase the risk for post-operative infections, and how antibiotics influence changes in the breast microbiome, we can manipulate these environments to optimize outcomes.

## Methods

### *Design*

This study is designed as a prospective cohort with an embedded randomized (non-blinded) control trial. 40 patients will form the cohort for our feasibility portion of the study. We are testing feasibility of our novel technique for obtaining breast microbiome samples. Patients who are scheduled to undergo mastectomy for breast cancer treatment with implant-based breast reconstruction will be recruited to be a part of the cohort. All of these patients will undergo the same microbiome sampling protocol, which includes taking samples of the breast microbiome once intra-operatively and then weekly for four weeks post-operatively during clinic visits. All patients will be followed for at least 90 days for endpoints, with the primary endpoint being development of post-operative infection.

Randomized-control component: All patients will receive the standard pre-incision antibiotics as well as standard perioperative antibiotics. They will then be randomized (using block randomization in groups of four participants per block) to receive the standard post-operative antibiotic treatment (Cohort A, n=20) or to receive only the standard 24 hours of perioperative antibiotics (Cohort B, n=20).

### *Subjects and Variables*

The target population in this study is all women undergoing mastectomy with implant-based reconstruction, specifically staged implant-based reconstruction in which a two-port tissue expander is used in the first stage of the reconstruction (one port fills the expander, one port allows for aspiration of peri-expander fluid). The accessible population is the subset of this target population that is treated by breast and reconstructive surgeons at the UCSF Breast Care Center. Our study population will be sampled by convenience sampling in a consecutive design. We will recruit all eligible patients seen by our two breast reconstructive surgeons at the UCSF

Breast Care Center, beginning in September, 2021. All enrolled patients will be followed in clinic for at least 90 days post-operatively.

*Inclusion Criteria*

1. Patients must have histologically confirmed breast malignancy
2. Age ≥ 18 years
3. Scheduled to undergo mastectomy with the immediate placement of tissue expanders
4. Ability to understand a written informed consent document, and the willingness to sign it
5. At least 4 weeks post-completion of chemotherapy or radiation

*Exclusion Criteria*

1. Any significant medical condition or laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
2. Pregnant or breastfeeding
3. Patients who have taken antibiotics within 90 days of the consent date
4. Patients who have taken probiotics within 90 days of the consent date
5. Patients who have a documented or reported allergic reaction to the outlined antibiotics to be used in this study

***Measurements***

*Predictor and Outcome Variables:*

The predictors in this study are both the baseline microbiome and the receipt or non-receipt of antibiotics. The primary outcome is development of post-operative implant infection within 90 days.

*Measurement of Variables:*

Receipt or non-receipt of antibiotics will be measured as a dichotomous variable. Infection will be measured as a dichotomous variable, however in the analysis phase, we will consider analyzing this as an ordinal variable (mild, moderate, severe) based on whether the infection was treated with oral antibiotics, IV antibiotics, or IV antibiotics and removal of implant.

We will compare the microbiomes between groups and the evolution of the breast microbiome over time as follows –

Diversity: Alpha diversity will be evaluated for species richness by number of operational taxonomic units and for evenness using the Shannon Index. Beta diversity will be evaluated by using the Bray Curtis index graphically visualized with the Principal Coordinates Analysis to identify community differences between groups.

Microbial composition: Microbial composition will be evaluated by grouping identified microbes into operational taxonomic units at the species, genera and phyla levels. We will compare the relative abundances of these microbes between groups at the species, genera, and phyla levels using the Kruskal-Wallis test and weighted and unweighted analyses.

*Enhancing Causal Inference:*
We have proposed a randomized, non-blinded clinical trial. Therefore the investigators, providers, and subjects will know the treatment administered. We have chosen not to blind this trial in order to be able to efficiently make treatment decisions in the case in which participants develop evidence of post-operative infection, which is a common outcome after this procedure (incidence is ~ 15%). Two arms will be tested. Patients will be block randomized in groups of four to either receive or not receive post-operative antibiotics. We have chosen block randomization in groups of four so that the number of patients in each cohort is roughly equal at all times, in the case we need to stop our trial early.

We will use a random number generator in order to block randomize patients in groups of four with two of the patients in each group randomized to receive post-operative antibiotics and two of the patients in each group randomized not to receive post-operative antibiotics. We do not see a need to stratify the blocks for randomization at this time. The design of our study is not amenable to a run-in design, as treatment starts after a surgical procedure and is time-sensitive.

Although we will not be blinding our trial, we will have at least two providers assess each participant at each follow-up visit in order to assess for development of clinical infection or other post-operative complications.

*Questionnaire:*
In breast reconstruction surgery, the most respected questionnaire is the BREAST-Q (Appendix A). We plan to administer this questionnaire to our study participants. Several papers have validated the questionnaire in multiple populations. The BREAST-Q framework has been validated for patients undergoing breast conserving therapy, mastectomy, and reconstruction, as well as other breast procedures. Each module assesses two domains and 6 sub-domains. The two domains assessed are Health-Related Quality of Life and Patient Satisfaction. The six sub-themes are QOL: Psychosocial, Physical, and Sexual Well-being; and Patient Satisfaction: Satisfaction with Breasts, Satisfaction with Outcome, Satisfaction with Care. We are particularly interested in how patients who experience complications (particularly infections) respond differently to this questionnaire when compared to those who do not experience complications.

We plan to administer the version of this questionnaire that is specific to breast reconstruction. Although the questionnaire appears quite long, only a subset of the questions apply to patients in our study. We expect the questionnaire to take 5-10 minutes to complete, and we will provide it to patients during a post-operative visit while they are awaiting the care of a provider.

**Statistics**
*Hypotheses:*

Null Hypothesis: The rate of severe implant infections is equal in patients who receive post-operative antibiotics compared to patients who do not receive post-operative antibiotics.

Alternative Hypothesis: The rate of severe implant infections is higher in patients who receive post-operative antibiotics compared to patients who do not receive post-operative antibiotics. (two-sided)

*Sample size/Analysis Plan:*
The statistical test used for a dichotomous predictor and a dichotomous outcome, such as will be used in this study, is the chi-squared test. The null and alternative hypotheses are outlined above. We are assuming that 10% of patients receiving post-operative antibiotics develop severe implant infections. This is based on literature reporting 5.8 to 28% infection rate in this population, combined with our center's experience that patients require explant of implants when they develop any clinical infection in approximately half of cases. We want to be able to detect a difference if only 5% of patients not receiving post-operative antibiotics develop severe post-operative implant infections. The effect size is therefore 5%. Setting alpha = 0.05 (two-sided) and beta = 0.80, the required sample size is 473 per group (475 using online calculator). This large of a sample size is not totally realistic in a single center study, although it could be realistic over several years at a single center or in a multi-center study.

As this is a pilot feasibility study, we are recruiting 40 patients total (20 in the treatment arm and 20 in the control arm). This is based off of a goal pilot study recruitment time period of 6 months. The PI in this study performs approximately three of these procedures per week. Accounting for unwillingness to participate (~40-50%), we therefore estimate we can successfully recruit 40 patients to our pilot study in 6 months.

**Ethical Issues**
*Safety Assessments:*
Safety will be assessed by reviewing laboratory evaluations, physical examination, and spontaneous report. Each patient will be assessed periodically for the development of signs or symptoms of infection. If any patient in the non-treatment group develops signs or symptoms of infection, she will be promptly prescribed antibiotics and undergo a full work-up appropriate for her clinical condition. We expect the infection rates to be comparable between groups (15-20%). Therefore we predict the probability of having to stop the study early is 5-16% as outlined below.
Stopping rule: We will continuously be assessing both groups for clinical signs of infection. If the infection rate in Cohort B reaches or exceeds 33%, we will deem the study unsafe and stop the study. This will be initially be tabulated when n=10 and in the control group.

| Stopping rule | n=10 | n=15 |
|---|---|---|
| probability if infection rate w/o antibiotics is | 4 or more | 5 or more |
| 15% | 5% | 6% |
| 20% | 12% | 16% |
| 33% | 43% | 59% |

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## BREAST-Q™ – BREAST CANCER CORE SCALE (PRE- AND POSTOPERATIVE) VERSION 2.0: PSYCHOSOCIAL WELL-BEING

With your breast area in mind, in the past week, how often have you felt:

| | None of the time | A little of the time | Some of the time | Most of the time | All of the time |
|---|---|---|---|---|---|
| a. Confident in a social setting? | **1** | **2** | **3** | **4** | **5** |
| b. Emotionally able to do the things that you want to do? | **1** | **2** | **3** | **4** | **5** |
| c. Emotionally healthy? | **1** | **2** | **3** | **4** | **5** |
| d. Of equal worth to other women? | **1** | **2** | **3** | **4** | **5** |
| e. Self-confident? | **1** | **2** | **3** | **4** | **5** |
| f. Feminine in your clothes? | **1** | **2** | **3** | **4** | **5** |
| g. Accepting of your body? | **1** | **2** | **3** | **4** | **5** |
| h. Normal? | **1** | **2** | **3** | **4** | **5** |
| i. Like other women? | **1** | **2** | **3** | **4** | **5** |
| j. Attractive? | **1** | **2** | **3** | **4** | **5** |



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**Note to Investigators:** This scale can be used independently of the other scales. This scale is exactly the same across the three Breast Cancer Preoperative and Postoperative Modules (i.e. Mastectomy, Reconstruction, and Breast Conserving Therapy).

## BREAST-Q™ - BREAST CANCER CORE SCALE (PRE- AND POSTOPERATIVE) VERSION 2.0: SEXUAL WELL-BEING

Thinking of your sexuality, how often do you generally feel:

| | None of the time | A little of the time | Some of the time | Most of the time | All of the time |
|---|---|---|---|---|---|
| a. Sexually attractive in your clothes? | **1** | **2** | **3** | **4** | **5** |
| b. Comfortable/at ease during sexual activity? | **1** | **2** | **3** | **4** | **5** |
| c. Confident sexually? | **1** | **2** | **3** | **4** | **5** |
| d. Satisfied with your sex-life? | **1** | **2** | **3** | **4** | **5** |
| e. Confident sexually about how your breast area looks when unclothed? | **1** | **2** | **3** | **4** | **5** |
| f. Sexually attractive when unclothed? | **1** | **2** | **3** | **4** | **5** |



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**Note to Investigators:** This scale can be used independently of the other scales. This scale is exactly the same across the three Breast Cancer Preoperative and Postoperative Modules (i.e. Mastectomy, Reconstruction, and Breast Conserving Therapy).The following statement can be added to the stem to provide an opportunity for the patient to decline completing this scale. 'The following questions ask about your sexual well-being. If you are uncomfortable answering these questions or do not feel that they apply to you, please check the box and skip the questions that follow.'

## BREAST-Q™ - BREAST CANCER CORE SCALE (PREOPERATIVE) VERSION 2.0: SATISFACTION WITH BREASTS

With your breast area in mind, in the past week, how satisfied or dissatisfied have you been with:

| | Very Dissatisfied | Somewhat Dissatisfied | Somewhat Satisfied | Very Satisfied |
|---|---|---|---|---|
| a. How you look in the mirror clothed? | **1** | **2** | **3** | **4** |
| b. How comfortably your bras fit? | **1** | **2** | **3** | **4** |
| c. Being able to wear clothing that is more fitted? | **1** | **2** | **3** | **4** |
| d. How you look in the mirror unclothed? | **1** | **2** | **3** | **4** |



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**Note to Investigators:** This scale can be used independently of the other scales.

## BREAST-Q™ - RECONSTRUCTION MODULE (POSTOPERATIVE) VERSION 2.0: SATISFACTION WITH BREASTS

If you have had a mastectomy and reconstruction of both breasts, answer these questions thinking of the breast you are least satisfied with. With your breasts in mind, in the past week, how satisfied or dissatisfied have you been with:

| | Very Dissatisfied | Somewhat Dissatisfied | Somewhat Satisfied | Very Satisfied |
|---|---|---|---|---|
| a. How you look in the mirror clothed? | **1** | **2** | **3** | **4** |
| b. The shape of your reconstructed breast(s) when you are wearing a bra? | **1** | **2** | **3** | **4** |
| c. How normal you feel in your clothes? | **1** | **2** | **3** | **4** |
| d. The size of your reconstructed breast(s)? | **1** | **2** | **3** | **4** |
| e. Being able to wear clothing that is more fitted? | **1** | **2** | **3** | **4** |
| f. How your breasts are lined up in relation to each other? | **1** | **2** | **3** | **4** |
| g. How comfortably your bras fit? | **1** | **2** | **3** | **4** |
| h. The softness of your reconstructed breast(s)? | **1** | **2** | **3** | **4** |
| i. How equal in size your breasts are to each other? | **1** | **2** | **3** | **4** |
| j. How natural your reconstructed breast(s) looks? | **1** | **2** | **3** | **4** |
| k. How naturally your reconstructed breast(s) sits/hangs? | **1** | **2** | **3** | **4** |
| l. How your reconstructed breast(s) feels to touch? | **1** | **2** | **3** | **4** |
| m. How much your reconstructed breast(s) feels like a natural part of your body? | **1** | **2** | **3** | **4** |
| n. How closely matched (similar) your breasts are to each other? | **1** | **2** | **3** | **4** |
| o. How you look in the mirror unclothed? | **1** | **2** | **3** | **4** |



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**Note to Investigators:** This scale can be used independently of the other scales.

## BREAST-Q™ - RECONSTRUCTION MODULE (POSTOPERATIVE) VERSION 2.0: SATISFACTION WITH IMPLANTS

If you have implants in both breasts, answer these questions thinking of the breast you are least satisfied with. In the past week, how satisfied or dissatisfied have you been with:

| | Very Dissatisfied | Somewhat Dissatisfied | Somewhat Satisfied | Very Satisfied |
|---|---|---|---|---|
| a. The amount of rippling (wrinkling) of your implant(s) that you can see? | **1** | **2** | **3** | **4** |
| b. The amount of rippling (wrinkling) of your implant(s) that you can feel? | **1** | **2** | **3** | **4** |



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**Instructions**: These questions should be considered as stand-alone. Thus, the patient's response is taken as the score for each item. Higher scores reflect a better outcome.

**Note to Investigators:** This scale can be used independently of the other scales and should only be completed by patients who have had reconstruction using implants. The following statement can be added to the stem to provide an opportunity for the patient to decline completing this scale. 'If you do not have implants, please check the box and skip the questions that follow.'

## BREAST-Q™ - BREAST CANCER CORE SCALE (PRE- AND POSTOPERATIVE) VERSION 2.0: PHYSICAL WELL-BEING: CHEST

In the past week, how often have you experienced:

| | None of the time | Some of the time | All of the time |
|---|---|---|---|
| a. Pain in the muscles of your chest? | **1** | **2** | **3** |
| b. Difficulty lifting or moving your arms? | **1** | **2** | **3** |
| c. Difficulty sleeping because of discomfort in your breast area? | **1** | **2** | **3** |
| d. Tightness in your breast area? | **1** | **2** | **3** |
| e. Pulling in your breast area? | **1** | **2** | **3** |
| f. Nagging feeling in your breast area? | **1** | **2** | **3** |
| g. Tenderness in your breast area? | **1** | **2** | **3** |
| h. Sharp pains in your breast area? | **1** | **2** | **3** |
| i. Aching feeling in your breast area? | **1** | **2** | **3** |
| j. Throbbing feeling in your breast area? | **1** | **2** | **3** |

Post-operative only

| | | | |
|---|---|---|---|
| k. Swelling of the arm (lymphedema) on the side(s) that you had your breast surgery? | **1** | **2** | **3** |



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**Note to Investigators:** This scale can be used independently of the other scales.

## BREAST-Q™ - RECONSTRUCTION MODULE (POSTOPERATIVE) VERSION 2.0: PATIENT EXPERIENCE: SATISFACTION WITH INFORMATION

How satisfied or dissatisfied were you with the information you received from your surgeon about:

| | Very Dissatisfied | Somewhat Dissatisfied | Somewhat Satisfied | Very Satisfied |
|---|---|---|---|---|
| a. How the breast reconstruction surgery was to be done? | **1** | **2** | **3** | **4** |
| b. Healing and recovery time? | **1** | **2** | **3** | **4** |
| c. Possible complications? | **1** | **2** | **3** | **4** |
| d. The options you were given regarding types of breast reconstruction? | **1** | **2** | **3** | **4** |
| e. The options you were given regarding timing of your breast reconstruction (i.e., same time as your mastectomy versus later)? | **1** | **2** | **3** | **4** |
| f. The pros and cons of the timing of your breast reconstruction? | **1** | **2** | **3** | **4** |
| g. How long the process of breast reconstruction would take from start to finish? | **1** | **2** | **3** | **4** |
| h. What size you could expect your breasts to be after reconstructive surgery? | **1** | **2** | **3** | **4** |
| i. How much pain to expect during recovery? | **1** | **2** | **3** | **4** |
| j. What you could expect your breasts to look like after surgery? | **1** | **2** | **3** | **4** |
| k. How long after reconstruction surgery it would take to feel like yourself/feel normal again? | **1** | **2** | **3** | **4** |
| l. How the surgery could affect future breast cancer screening (e.g., mammogram, self-examinations)? | **1** | **2** | **3** | **4** |
| m. Lack of sensation in your reconstructed breast(s) and nipple(s)? | **1** | **2** | **3** | **4** |
| n. What other women experience with their breast reconstruction surgery? | **1** | **2** | **3** | **4** |
| o. What the scars would look like? | **1** | **2** | **3** | **4** |



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**Note to Investigators:** This scale can be used independently of the other scales. Depending on the use of this scale, you may wish to add the following statement to the stem for clarity. 'These questions ask about the surgeon who performed your most recent surgery.'