Bacterial Decolonization to Prevent Radiation Dermatitis: A Randomized Controlled Trial and Quality of Life Assessment

NCT #03883828

Study Protocol

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Table of Contents

1. Description of the study:

The purpose of this study is to determine whether bacterial decolonization of the nares and skin prior to treatment with radiotherapy (RT) for patients with cancers of the head and neck or breast, can prevent high-grade radiation dermatitis (RD) and improve quality of life. This study is being conducted because prior studies from this research group have found bacterial colonization in the nose prior to initiation of RT to be associated with an increased risk of high grade RD. Patients in the treatment arm will receive pretreatment with mupirocin ointment to the nares and chlorhexidine gluconate wash to the body, while patients in the control arm will receive standard of care treatment. Bacterial cultures will be taken from the nares, radiated skin, and site contralateral to radiation at baseline and at completion of RT from all participants. If severe infection requiring systemic antibiotics occurs, we may obtain additional cultures. Participants will also participate in a quality of life questionnaire before and after RT.

2. Background:

RD is a common and often debilitating adverse event associated with the use of fractionated external beam RT for the treatment of numerous cancers. RD may occur within hours to weeks of exposure to radiation and often worsens throughout the course of treatment.[1] Symptoms include itching and pain which can severely affect quality of life.[2] RD occurs in up to 95% of patients who receive RT for curative cancer treatment and rates are highest amongst patients treated for breast, head and neck, and anogenital cancers.[3] The most commonly used grading instrument for RD, the Common Terminology Criteria for Adverse Events (the CTCAE), grades RD on a scale of 0-5, with higher grades indicating more severe involvement as seen in figure 1.[4]

Direct damage to keratinocytes in addition to local inflammation are proposed to cause RD, however the pathogenesis of the subsequent inflammation is not well understood. One proposition is that bacteria on the skin may increase the risk of severe RD by increasing inflammation and preventing the natural re-epithelialization of the keratinocytes exposed to radiation.[5] Several case reports have shown that secondary infection with bacteria such as Staphylococcus Aureus (SA) has been implicated in RD, and they propose that bacteria exacerbates dermatitis via activation of MHC class II molecules on immune cells.[1] The association between SA infection and RD was also confirmed in a small study which found that 23% of RD patients had secondary skin infections and that a large subset of those patients (57%) developed grade 4 RD.[6]

In a recent study, our group discovered that nasal colonization with any bacteria and specifically with SA prior to RT was a powerful predictor of high-grade RD. Further supporting the role of bacteria in the pathogenesis of RD, we found more SA on the radiated skin after treatment in patients with high grade RD. These findings were consistent with similar results in other inflammatory skin diseases such as atopic dermatitis and mycosis fungoides, where SA has been shown to play an important role in skin inflammation.[7,8] Prior studies have not looked at bacterial decolonization as a strategy to prevent RD. The goal of this study is to assess the efficacy of bacterial decolonization in patients prior to and during RT. The study outcomes have the potential to change the way we approach prevention of RD in cancer patients.

Universal bacterial decolonization using similar strategies to what we are proposing have been shown to be safe and cost effective in other disease states, and is

now the standard of care in the intensive care unit and prior to orthopedic surgery in order to prevent infectious complications. For example, Huang et al found that universal SA decolonization with chlorhexidine and mupirocin dramatically decreased methicillin resistant staphylococcus aureus (MRSA) prevalence and MRSA-associated hospitalizations in a county-wide study.[9] A recent systematic review of 19 studies showed that there was a reduction in surgical site infections and wound complications after institution of a SA screening and decolonization protocol.[10]

This study will focus on preventing RD in patients with breast and head/neck cancer, as these cancer types are associated with the highest incidence of RD. Anogenital cancers will not be included in this study, as too few patients from this category were recruited in our preliminary study to achieve statistical significance. Furthermore, this study excludes patients receiving RT for palliative intent as these patients receive few treatments and are unlikely to develop radiation dermatitis. By implementing a similar decolonization protocol in patients receiving RT, we hope to prevent the development of RD and improve quality of life.

3. Objectives and endpoints:

1. The primary goal is to determine if bacterial decolonization prior to RT prevents development of high grade RD (grade 2-5). The primary endpoint is the incidence of high grade RD at the end of the trial.
2. The secondary goal is to assess if the intervention improves quality of life compared to the control arm. The secondary endpoint is the quality of life, assessed by the Skindex-16.

4. Study Design:

4.1 Subject inclusion criteria:

1. Age ≥ 18
2. Diagnosis of a solid tumor of the breast or head and neck with plans for fractionated RT (≥ 15 fractions) with curative intent, including post-operative patients deemed eligible for RT by their surgeons and radiation oncologists

4.2 Patient exclusion criteria:

1. Prior RT to the region of interest
2. Existing dermatologic condition affecting the treatment area (eg: atopic dermatitis, psoriasis, and non-healing wounds)
3. Known allergy to chlorhexidine or mupirocin

4.3 Recruitment:

Patients will be recruited from the Montefiore-Einstein Department of Radiation Oncology. Study physicians will identify patients seen in their clinics that meet the study's inclusion criteria. We aim to recruit up to 80 patients for the study. Adult patients with breast or head and neck cancer receiving curative radiation therapy will be eligible for the study. There will be no compensation for the study.

4.4 Study Procedures

This trial will be a randomized controlled trial assessing the efficacy of universal bacterial decolonization in preventing high-grade RD. Therefore, all participants, regardless of baseline culture results, will be 1:1 randomized to one of two arms: the intervention arm and the control arm. The randomization will be performed in a stratified manner within each of the two cancer types (breast cancer or head and neck cancer).

All patients, regardless of treatment arm, will receive a complete history and physical exam during their screening visit. Patients in the control arm will be treated according to standard of care without any RD prophylaxis. Patients in the intervention arm will receive a decolonization regimen, which is accepted as standard of care and commonly used in other patient populations (ICU and prior to orthopedic surgery). The decolonization regimen will consist of intranasal mupirocin ointment to be applied twice daily to the nares and chlorhexidine wash to be used once daily to the body. This combined regimen will be conducted by the patient for 5 consecutive days prior to the start of RT, and will be repeated for an additional five days every 2 weeks for the duration of RT, according to standard of care decolonization methods.[9] Should a patient experience an adverse reaction to the topical chlorhexidine gluconate solution or mupirocin ointment, the principal investigator may discontinue their participation from the study and, depending on severity of adverse effect, remove the offending agent and treat any resulting rash or skin discomfort. This will not affect their radiation therapy treatment, and they will continue to receive standard of care radiation therapy.

Chlorhexidine and mupirocin will be prescribed by the principal investigator prior to the start of radiation therapy, at no cost to the patient. Patients will be supplied with a calendar showing the dates of decolonization and asked to document their decolonization regimen to monitor for compliance. Standardized photographs of the radiated area will be taken at baseline, and at the end of RT for purposes of grading. Should a patient refuse photographs, they may still participate in the study. Grading scores from the treating radiation oncologist's note in the electronic health record will be used in place of clinical photographs. Research funds from the division of dermatology and radiation oncology will be used to pay for bacterial culture swabs, wound culture laboratory fees, mupirocin, and chlorhexidine solutions. Should a patient in any treatment arm develop symptomatic RD or RD that is grade 2 or higher, the patient will be treated by the radiation oncologist. There is no restriction on use of topical or oral antibiotics as needed during the study. Patients may be treated by the radiation oncologist with other topical preparations including Aquaphor and/or silver sulfadiazine regardless of treatment arm.

The SKINDEX-16 questionnaire will be used prior to initiation of RT and at completion of RT to assess whether decolonization can improve patient quality of life. Validated in 2001, this questionnaire assesses domains of symptoms, emotions, and functioning. This questionnaire is commonly used in the evaluation of dermatologic diseases including RD, as it has demonstrated both content and construct validity in previous studies.[11] For example, one recent clinical trial that assessed mometasone furoate for the prevention of RD in breast cancer patients also utilized the SKINDEX-16 to assess quality of life as a secondary measure.[12] Furthermore, our preliminary study showed that patients with more severe RD were impacted more severely than patients without RD in all three domains (data submitted for publication).

Finally, de-identified samples from superficial skin swabs will be placed in a storage buffer meant to preserve bacterial nucleotides and kept in a freezer at -80C for

future microbiome analysis. Bacterial RNA and DNA will then be extracted from the samples in order to perform skin microbiome analysis via whole-community metagenomics sequencing and RNA transcriptomics sequencing. Of note, only bacterial samples from culture swabs will be stored for future microbiome analysis of the skin flora. No DNA from participants will be stored.

Study evaluations will include:

Before RT and within two weeks of completion of RT:

- Bacterial cultures obtained via a superficial swab from (1) the nares, (2) skin at the irradiated site and (3) contralateral or other non-radiated skin. This is a non-invasive test using a cotton-tipped applicator inserted into the nostrils or rubbed on the skin.
- Superficial swabs from the same 3 sites will be obtained in the same manner to be stored in a -80° C freezer for future de-identified microbiome analyses.
- Standardized photographs of skin at radiated site to be graded by a dermatologist blinded to study arm. Additional photographs or notes from the chart may be taken in the case of that severe RD develops during treatment.
- Quality of Life assessment using the Skindex-16 questionnaire.[10]

Before and during RT:

- Patients will be asked to initial each date on the supplied calendar when they complete the decolonization protocol in order to assess compliance.

4.5 Study Calendar and Study Timeline

Study Calendar:

	Screening	Pre-RT (-5 days)	Radiation Therapy Week 2	Radiation Therapy Week 4	Radiation Therapy Week 6 (if applicable)	Radiation Therapy Week 8 (if applicable)	Last day of RT or within 2 weeks of RT completion
Informed Consent	X						
Complete History and Physical	X						X
Randomization	X						
Bacterial Culture Swabs*	X						X
Photographs of skin at radiated site	X						X
Skindex-16 Questionnaire	X						X
Decolonization Regimen		XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	
Patient Medication Calendar**	X	X	X	X	X	X	

* Bacterial cultures obtained via a superficial swab from (1) the nares, (2) skin at the irradiated site and (3) contralateral or other non-radiated skin. This is a non-invasive test using a cotton-tipped applicator inserted into the nostrils or rubbed on the skin,

** A member of the study team will provide the patient with medication calendars prior to the start of each prescribed regimen, and review for compliance throughout treatment. Patients will be asked to initial each date on the supplied calendar when they complete the decolonization protocol in order to assess compliance.

Study Timeline:

	April 2019-April 2020	April 2020 - December 2020
Subject Enrollment	X	
Data Collection	X	X
Statistical Analysis		X
Results Reporting		X

4.6 Consent

Consent will be performed in the Montefiore-Einstein Center for Cancer Care Radiation Oncology clinics. The study PI, co-investigators, and key personnel will all participate in providing the informed consent to possible study participants. Study key personnel, which includes the treating radiation oncologists, will identify eligible patients. These personnel will then explain the study, explain the consent form, ask the patient if they have any questions, and confirm that they are willing to participate in the study.

5.1 Statistical Plan and Power Analysis

All analyses will be performed according to intention to treat, where patients are analyzed as randomized. The study statistician will conduct randomization and the study coordinator will hold the randomization key. Baseline characteristics will be compared between the interventional arm and the control arm using 2-sample t-tests for continuous variables and using Pearson's chi square or Fisher's exact tests for categorical variables. Primary endpoint analysis: The primary study endpoint is development of higher grade radiation dermatitis (RD) (grade 2-5) compared to lower grade RD (grade 0-1) during the course of external beam radiotherapy. While grades 3-5 are normally considered "high-grade radiation dermatitis," we will be considering and analyzing grades 2-5 as "higher grade radiation dermatitis" versus grades 0-1 as "lower grade dermatitis." No patients in our previous study experienced grades 4-5 radiation dermatitis, so this grouping will be performed for ease of statistical analysis. Pearson's chi square or Fisher's exact tests will be used to compare the incidence rates of high-grade (grade 2-5) radiation dermatitis between the interventional arm and the control arm to assess whether the intervention is

associated with a lower incidence rate of high-grade RD. Logistic regression models will be used to assess this association while adjusting for covariates including age, gender, BMI, cancer type, radiation dose, and concurrent chemotherapy.

Secondary endpoint analysis: Secondary endpoint, quality of life (QoL), will be assessed before and after the radiotherapy. Paired t-tests will be used to compare the QoL summary score between baseline and at the end of the trial within each arm. The 2-sample t-test will be used to compare the QoL score change from baseline to the end of radiotherapy between the two arms. Linear regression models will be used to compare the changes in QoL scores between the 2 arms while adjusting for covariates including age, gender, BMI, cancer type, radiation dose, and concurrent chemotherapy. Missing data will be minimized by pre-emptively implementing effective participant follow-up strategies and by ensuring optimal data collection. In the subsequent analyses, we will evaluate the type and mechanisms of missing data, for example whether it is missing at random (MAR). Multiple imputations may be used to impute missing data. Results obtained from data with imputation will be compared to those obtained from complete data to assess the influence of missing data. Reasons and characteristics of loss-to-follow-up will be documented and examined in order to assess the extent to which patient attrition could bias our results.

Power Analysis: Based on previous studies, we expect that ~50% of our recruited patients will have breast cancer and ~50% will have head/neck cancer. To control for this, we plan to randomize patients in a stratified manner, so that 30 patients with each subtype of cancer will be recruited into each arm (interventional and control arm). With 30 patients in the interventional arm and 30 patients in the control arm, assuming a significance level (alpha) of 0.05, the study has 0.80 power to detect a minimum difference of 0.29 in the incidence of Grade 2-5 radiation dermatitis between the arms using 2-sided test. The sample size was calculated based on results from a previous study from our lab, in which the incidence rate of grade 2-3 radiation dermatitis in the control arm was 0.38. Assuming a conservative 25% attrition rate in the study, we plan to recruit a total of 80 patients (40 each arm) in order to ensure a final sample size of 60 (30 each arm).

6. Data Monitoring and Safety

6.1 Data Storage

Patient data and images will be entered into software on Montefiore clinic computers that are password protected where only study investigators and involved physicians will have access to the data. Patient identifying information will be recorded to allow for appropriate medical chart review, which will be important for the study's analyses. The clinic's data managers will help oversee that all patient data and information is protected and confidential. All patients will receive an identification code that will be kept in a password protected excel spreadsheet associated with their MRN. All other patient study information will be kept separate from any of their identifying information.

6.2 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.
- In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

6.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

6.4 Adverse Event Monitoring and Reporting

As this is an interventional protocol, any adverse events will be recorded and reported. Both mupirocin and chlorhexidine are topical medications that are routinely used in the hospital setting, therefore few adverse events are expected. Because this is small single site study with no more than minimal risk expected, the study principle investigator (PI) will monitor closely for adverse events. The treating radiation oncologist will assess for adverse events at each radiotherapy visit as well. Any unanticipated or serious events (grade 3 or higher) related to participation in this study will be investigated by the study PI and reported to the Einstein IRB. All adverse events will be recorded in an electronic document that is de-identified. This adverse events log, attached in the appendix, will then be submitted to the IRB at the time of protocol renewal.

Unanticipated problems, defined by the Office for Human Research Protections (OHRP) include any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Any incident that meets all three criteria will be reported study and clinic staff to the Principle Investigator within 48 hours. All serious events related to study participation and death among participants will be reported to the Einstein IRB via:

Phone: 718.430.2237
Email: irb@einstein.yu.edu

Events that require reporting will be graded according to the CTCAE version 5.0. All study related clinic sites have access to this form and it can be downloaded at http://ctep.cancer.gov.

Already in place in and distinct from the study, all safety monitor and reporting will be done by the standard of care and protocols of the Montefiore Center for Cancer Care and department of radiation oncology. There will be no Data Monitoring Committee. Any serious events will be reported to both the study PI and IRB.

The study PI, co-investigators and key personnel will be charged with assuring data accuracy and protocol compliance, interim monitoring of accumulated data from research activities to assure the continuing safety of participants, relevance of the study question, appropriateness of the study, and integrity of the accumulating data.

7. Appendix

Figure 1. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for Radiation Dermatitis

Injury, poisoning and procedural complications					
CTCE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation; mostly confined to skin folds and creases; moderate erythema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death

*Dermatitis Radiation Definition: A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective doses of ionizing radiation
*Navigational Note: Synonym: Radiation induced skin toxicities (CTCAE v3.0)

Figure 2. Skindex-16

kindex16

THESE QUESTIONS CONCERN THE SKIN CONDITION WHICH HAS BOTHERED YOU THE MOST DURING THE PAST WEEK

During the past week, how often have you been bothered by:	Never Bothered ↓						Always Bothered ↓
1. Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Your skin condition **burning** or **stinging**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Your skin condition **hurting**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Your skin condition **being irritated**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. The **persistence / reoccurrence** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. **Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. The **appearance** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. **Frustration** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. **Embarrassment** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Being annoyed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Your skin condition making it hard to **show affection**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. The effects of your skin condition on your **daily activities**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Your skin condition making it hard to **work or do what you enjoy**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Have you answered every item? Yes ☐ No ☐

Figure 3. Blank Study Calendar

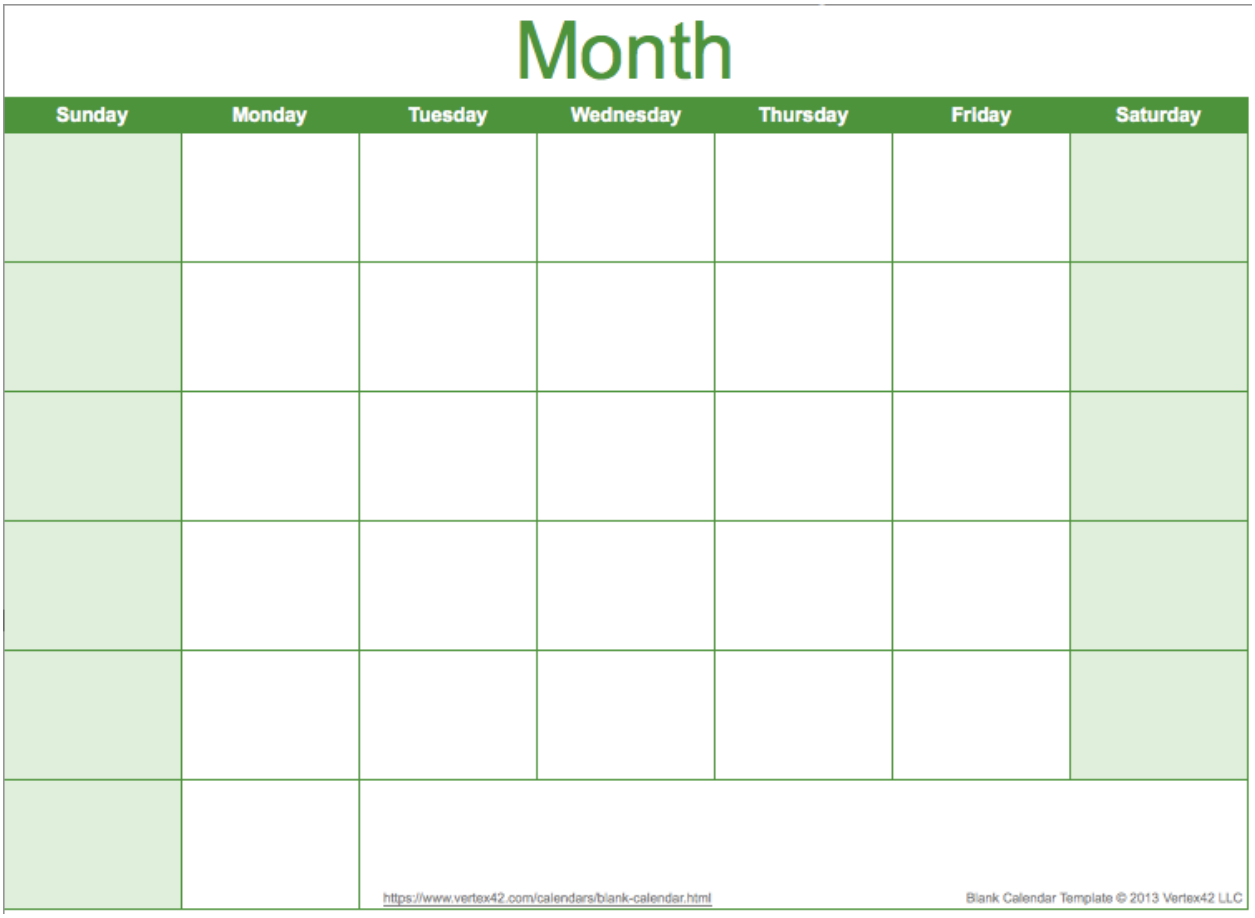


Figure 4. Patient Instructions

Bath Instructions

Shower or bathe with chlorhexidine (CHG) for 5 days in a row, beginning five days before your first radiation therapy session. Repeat for five days in a row, Monday-Friday, every 2 weeks for the duration of your treatment.

1. With each shower or bath, wash your hair as usual first with your regular shampoo. Do not use your regular shampoo after applying chlorhexidine.
2. Rinse your hair and body thoroughly after you shampoo your hair to remove the shampoo residue.
3. Apply the chlorhexidine (CHG) soap to your entire body ONLY FROM THE NECK DOWN. Do not use chlorhexidine (CHG) near your eyes or ears to avoid permanent injury to those areas. Do NOT apply chlorhexidine soap to deep, open wounds.
4. Turn water off and begin applying chlorhexidine soap. For the best effect, try to keep the chlorhexidine soap on skin as long as possible (2 minutes if you can) before rinsing off. While washing,
    a. Please pay special attention to the neck, armpit, groin, areas between the fingers and toes, and all skin folds, including under the breasts for women
    b. FIRMLY MASSAGE soapy sponge onto the areas below before placing back into the water

        ✓ Arms & Legs
        ✓ Chest & Back
        ✓ Abdomen
        ✓ Hip & Groin, then genitals & buttocks last

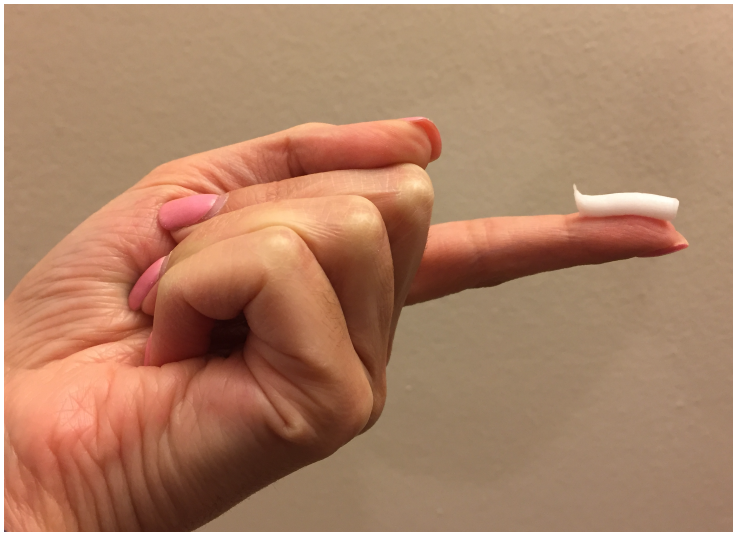
1. Turn the water back on and rinse your body thoroughly.
2. **Reapply soap a SECOND TIME to all skin areas from the neck down by FIRMLY MASSAGING as above.**
3. Rinse after 2 minutes and pat dry with a towel.

Allergic reactions and skin reactions are rare, but can occur. If you develop a rash or skin irritation that you believe is due to the chlorhexidine, discontinue use and contact our study staff at roya.nazarian@icahn.mssm.edu. **We encourage you to contact us if you are unsure and would like to discuss concerns with study staff.**
Severe allergic reactions are very rare, but can occur. If you develop an allergic reaction involving severe hives or have any difficulty breathing, call 911 or go to your nearest emergency department.

Mupirocin Nasal Ointment Instructions

Apply mupirocin ointment to nostrils twice daily for 5 days in a row. Repeat this 5-day course every 2 weeks, Monday-Friday, for the duration of your radiation therapy.

1. Wash hands prior to application of mupirocin ointment.
2. Apply a fingertip's length amount of ointment, as shown below, to a Q-tip.



3. Apply the Q-tip to the inside of both nostrils. Take care not to insert the Q-tip too far into your nostrils.
4. Close your nostrils by pressing the sides of the nose together and then releasing them. Do this over and over again for approximately 1 minute. You may also press the sides of the nose together and gently massage the nose.

Figure 5. Adverse Event Log

IRB #:				PI Name:								
Subject ID#	Date of Onset	Date Resolved	Outcome*	Seriousness**	Relationship***	Unanticipated (Y/N)	Action with Study Treatment ****	Reportable to Sponsor (Y/N)	Date Sent to Sponsor	Reportable to IRB (Y/N)	Date Sent to IRB	PI Initials and date
	Event Description:											
	Event Description:											
	Event Description:											
	Event Description:											
	Event Description:											
	Event Description:											

Key

***Outcome**
1. Resolved
2. Resolved with sequelae
3. Recovering
4. Not Recovered/Not Resolved
5. Fatal
6. Unknown

****Seriousness**
1. Fatal
2. Life-threatening
3. Serious
4. Not Serious

*****Relationship**
1. Definite
2. Probable
3. Possible
4. Unlikely

******Action with Study Treatment**
1. No Action
2. Interrupted
3. Discontinued

8. References

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