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Title: Mechanisms of Preventing Antibiotic-Associated Diarrhea and the Role for Probiotics

Document: Informed Consent Form

Document Date: June 22, 2019 (Approval)

Informed Consent for Clinical Research

Georgetown University

INSTITUTION: Georgetown University Medical Center

INTRODUCTION

You are invited to consider participating in this study. The study is called "Exploratory Pilot Studies to Demonstrate Mechanisms of Preventing Antibiotic-Associated Diarrhea and the Role for Probiotics." Please take your time to make your decision. Discuss it with your family and friends. It is important that you read and understand several general principles that apply to all who take part in our studies:

a) Taking part in the study is entirely voluntary;

b) Personal benefit to you may or may not result from taking part in the study, but knowledge may be gained from your participation that will benefit others; the purpose of this study is not to benefit you individually but to gain knowledge that may help others in the future.

c) You may decline to participate or you may withdraw from the study at any time without loss of any benefits to which you are entitled and without jeopardizing your access to care, treatment and health services unrelated to the research.

The purpose and nature of the study, possible benefits, risks, and discomforts, other options, your rights as a participant, and other information about the study are discussed below. Any new information discovered, at any time during the research, which might affect your decision to participate or remain in the study will be provided to you. You are urged to ask any questions you have about this study with the staff members who explain it to you. You are urged to take whatever time you need to discuss the study with your physician, hospital personnel and your family and friends. The decision to participate or not is yours. If you decide to participate, please sign and date where indicated at the end of this form.

The research is being sponsored by the National Center for Complementary and Integrative Health (NCCIH), a part of the National Institutes of Health (NIH). NCCIH is called the sponsor and Georgetown University, is being paid by NCCIH to conduct this study with Dr. Daniel Merenstein, MD as the principal investigator.

WHY IS THE STUDY BEING DONE?

The main purpose of this study is to better understand how consuming a probiotic ("friendly bacteria") can change or restore your gut microbiota (a collection of microorganisms –bacteria, fungi, viruses, etc.— which live in our gut and gastrointestinal tract) after it has been affected by antibiotic use. We will compare this to those who take a control yogurt without the added probiotic.

This research is being done because it has been shown that antibiotics typically decrease the number and type of bacteria in your gut microbiota, which may result in diarrhea. Sometimes probiotics are recommended to prevent diarrhea but we do not know exactly why or how your gut microbiota changes from the probiotic or from antibiotics.

One way that we can learn more about your microbiota is through fecal (stool) samples collected at different times before and during probiotic and antibiotic use. We will test your samples and measure any changes in the amount, number, and different types of microorganisms and short-chain fatty acids (SCFA), which are produced from fermentation, a digestive process that takes place in your intestines.

We hope by learning more about how probiotics and antibiotics affect your gut microbiota and SCFA, we will be able to help improve the health of patients taking antibiotics in the future.

You are being asked to participate in this study because you are a reasonably healthy adult. Additionally, you are eligible to participate in this study if:

1) You are between the ages of 18-65 years;

2) You are able to read, speak, and write in English;

3) You have access to a refrigerator for proper storage of the yogurt products; and

4) You have telephone access.

You may ***not*** participate in this study if any of the following apply to you: you have 1) diabetes or asthma that requires daily medication, 2) allergy to strawberry, 3) active diarrhea (defined as three or more loose stools per day for two consecutive days), 4) any gastrointestinal medications, i.e. medicines for irritable bowel syndrome, gastroesophageal reflux disease, inflammatory bowel disease, etc. (a full medication list will be reviewed by the study investigator before enrollment, 5) lactose intolerance, 6) history of heart disease, including valvulopathies or cardiac surgery, any implantable device or prosthetic, 7) history of gastrointestinal surgery or disease, 8) milk-protein allergy, 9) allergy to any component of the product or the yogurt vehicle, 10) allergy to penicillin or cephalosporin class antibiotics, 11) allergy to any of the following medications: a. penicillin, b. Erythromycin, c. Trimethoprim, d. Tetracycline, or e. Ciprofloxacin, or 12) currently breastfeeding, pregnant, or planning to become pregnant during the study.

You will also be asked to refrain from antibiotics and any probiotic foods or supplements for at least 30 days prior to the collection of first baseline stool sample until the completion of the 30-day study period. You will be supplied with a list of these products.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Approximately 60 subjects will be recruited from the Washington, DC metropolitan area for this study.

WHAT IS INVOLVED IN THE STUDY?

Once it is confirmed that you meet all inclusion and exclusion criteria, baseline data will be collected. These include your Baseline Health Status and Demographic Information

Once enrolled, you will be asked to avoid antibiotics and any probiotic foods or supplements for at least 30 days prior to starting the study (called the "run-in" period) until the completion of the 30-day study period. You will be asked to provide one stool sample before the run-in period, and one stool sample about 30 days after you enroll, prior to starting the antibiotics and yogurt. During this run-in period, we will also call twice to ask what you have eaten in the previous 24 hours (this is called a "diet recall"). You will collect stool samples multiple times throughout the study, one each on Days 7, 14, 21 and 30 (±2 days). Research staff will be trained on how to properly transport stool from your home and how to instruct you on collecting stool.

Following the baseline procedures and 30-day "run-in" period, we will confirm you still meet the inclusion and exclusion criteria and ask your Post Run-In Health Status. If you are still eligible, you will take a 7-day course of antibiotics, amoxicillin-clavulanate (875mg). You will also be "randomized" into one of the study groups: *Bifidobacterium animalis* subsp. *lactis* BB-12 (BB-12) probiotic supplemented yogurt, or control yogurt without the added probiotic. You will have a two in three chance of being placed in the probiotic group and a one in three chance of being in the control group. Neither you nor the investigator will know what group you are in.

You will then receive the probiotic yogurt or control yogurt for days 1 through 14 to be consumed by mouth once a day. The amount of probiotic supplemented yogurt drink to be supplied will be 4 ounces per day, which is slightly more than 100 grams/day. We will supply you with a measuring cup to measure the daily dose. During the initial visit, participants will also be given all the materials to collect stools, daily diary, and other study forms and materials, as well as the initial payment.

We will also ask a form called the Gastrointestinal Symptom Rating Scale (GSRS) on Days 1, 7, and 14 (±2 days), which is a quality of life questionnaire. Follow-up phone calls will be completed on Days 7, 14, and 30 (±2 days). It is important that all visits be completed on a timely and regular fashion. Generally, the Follow-Up Form will be the only form completed during the phone calls, but at times depending on your report, there may

be another form or two. The follow-up period includes all the time previous to the day of the interview. Any incidents that happen the day of the visit would be captured in the next follow-up visit.

There will be a set day that each subsequent visit should be completed for each participant. The research personnel will call at least one time per day for 3 business days or until the data is collected. If more than 3 business days have passed from the set day, you may be asked to provide any information at the next upcoming call.

You will keep a daily diary to track number of bowel movements, if antibiotic or yogurt was consumed on that day, number, shape and consistency of your stools, health, use of other medicines or products, adverse events, and quality of life.

Please advise the researchers of any medications you are taking. In addition, if you are taking any over-the-counter drugs or herbal supplements which you have obtained from the drug store, grocery store, etc., you should advise the researchers.

Timeline and Sample/Data Collection Schedule

Assessment	Pre Run-in Baseline	30-day Run-in	Post Run-in (0/+2)	1	7 (±2)	14 (±2)	21 (±2)	30 (±2)
Pre-screening (prior to baseline)								
Informed Consent Form & Process	X							
Inclusion/Exclusion Criteria	X		X					
Enrollment	X[a]							
Baseline Health Status	X							
Demographic Information	X							
Stool Sample Collection	X		X		X	X	X	X
Automated Self-Administered 24-Hour (ASA24) Dietary Assessment Tool (2 days)		X						
Run-in Period (30 days)		|→	→|					
Post Run-in Health Status			X					
Randomization			X					
Amoxicillin-clavulanate Intervention (7 days)				|→	→|			
Yogurt Intervention (14 days)				|→	→	→|		
Follow-up Data Collection/Phone Call					X	X		X
Daily Assessment Diary[b] (14 days)				|→	→	→|		
Gastrointestinal Symptom Rating Scale				X	X	X		
Adverse Event Reporting	|→	→	→	→	→	→	→	→|

[a]Enrollment will occur a minimum of 30 days prior to starting the interventions. Participants will provide one stool sample before the run-in period, refrain from antibiotics and probiotics during this period and provide 1 sample after the run-in period.
[b]Diary from days 1-14; information on stool number, shape and consistency, health, use of interventions, quality of life and adverse events.
X: collected on day; |→: starting from day; →|: through end day

The stool samples you collected throughout the study will be shared with two partner laboratories for testing. These tests will help us to learn more about any changes in your microbiota and short-chain fatty acids after taking the antibiotics and yogurt. The microbiota tests will be performed in Dr. Claire Fraser's laboratory at the Institute for Genome Sciences, a part of the University of Maryland School of Medicine, and the short-chain fatty acid tests will be performed in Dr. Maureen Kane's laboratory at the University of Maryland School of

Pharmacy. Any samples and data shared with our partners will only be identified by a unique study code, meaning that we will not share your name, address, or any information that can reveal your identity.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for approximately 8 weeks total. The first 30 days will be the period where you avoid all antibiotics and probiotic products (run-in). You will start the antibiotic and yogurt after these 30 days (called Day 1). You will finish taking the antibiotics on Day 7 and drinking the yogurt on Day 14. At days 21 and 30, you will be asked to provide stool samples as well as information about your health during this period. If you begin any antibiotics during the 30-day run-in period (but otherwise still qualify for the study), once you complete your antibiotics course we may ask you to extend your run-in period to a full 30 days before starting the yogurt.

The researcher may decide to take you off this study if circumstances arise concerning your medical best interest, funding is stopped, the treatment supplies are insufficient, your condition worsens, or new information become available.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

For trials of drugs or devices/procedures, there may be risks. You should discuss these with the research doctor and/or your regular doctor.

The most common risks and side effects related to the probiotic and non-probiotic cultured yogurt include: allergic reaction to drink ingredients, most likely strawberry, or digestive problems such as stomachaches or loose, watery bowels due to lactose intolerance.

Potential risks and side effects related to the amoxicillin-clavulanate administration most commonly include: nausea and/or vomiting, diarrhea, upset stomach and mild to severe skin rash.

The most serious potential risk is diarrhea caused by a *Clostridium difficile* infection. Occasionally, antibiotics result in an overgrowth of a potentially dangerous bacterium called "*Clostridium difficile*,' a bacterium that is naturally present in the guts of some humans. This is also known as '*C. difficile*' or '*C. diff*,' and can cause a severe and life-threatening diarrheal illness that may require additional medical treatment.

A small minority of patients who take an antibiotic will get an infection due to *C. difficile*, and some people, such as those over 65 years of age and those who have a history of gastrointestinal disease, have a greater risk for *C. difficile* infection than others. To minimize this risk, you may only enroll in this study if you are generally healthy, 65 years of age or under, and do not have gastrointestinal disease. Although all types of antibiotics can potentially result in a *Clostridium difficile* infection, the type of antibiotic used in this study is generally not considered as high risk for *Clostridium difficile* infection.

While severe *C. difficile* infections are rare, we will be asking you about your symptoms throughout the study. Symptoms of *C. difficile* infection include stomach pain or tenderness, bloody stools, fever, nausea, and diarrhea. If you experience symptoms you think may be due to *C. difficile* infection, call your personal doctor and alert them about your participation in this study. Please also alert a member of the study team.

Risks and side effects related to stool collection include: there is no known risk to stool collection. However, there may be some discomfort with collecting stool samples.

There may also be side effects, other than those listed above that we cannot predict. Other drugs may be given to make side effects that occur less serious and less uncomfortable. Many side effects may go away shortly after the yogurt consumption is stopped, but in rare cases side effects can be serious, long lasting or permanent.

Anyone who develops evidence of allergy or hypersensitivity to any component of the investigational product or treatment antibiotic will be withdrawn from the clinical study and receive no further doses of either probiotic or antibiotic. In addition, we will continue to follow these participants for safety for the remainder of the study.

For more information about risks and side effects, ask the researchers.

Risks associated with the genetic information:

Risks of participating in research involving genetic testing include the use of personal, genetic information for unauthorized or discriminatory purposes. All research personnel who will have access to genetic information about you are ethically and legally obligated to maintain the confidence of that information. However, there can be no absolute guarantees that the genetic information will remain confidential.

A new federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally offers the following protections:

Health insurance companies and employer-based group health plans may not request your genetic information that we get from this research.
Health insurance companies and employer-based group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009. The protections offered by GINA apply regardless of when the research that obtained the genetic information was conducted, even if prior to the effective date.

Be aware that this new law does not protect you against discrimination on the basis of your genetic information by companies that sell life insurance, disability insurance, or long-term care insurance. In addition, there is a risk that being in a genetics study can cause psychological distress or tension with other family members.

ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We cannot promise that you will personally experience medical benefits from participating in this study. The main purpose of this study is to gain knowledge on how probiotics and antibiotics affect the gut microbiota and SCFA, We hope the information learned from this study will benefit others in the future.

WHAT OTHER OPTIONS ARE THERE?

The only other option is to not participate in this study.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to protect your medical records and other personal information to the extent allowed by law. However, we cannot guarantee absolute confidentiality. The medical records of research study participants are stored and kept according to legal requirements. You will not be identified in any reports or publications resulting from this study. In addition to the researchers and research institution(s) conducting this study, organizations that may request to inspect and/or copy your research and medical records for quality assurance data analysis and other research related and operational or administrative purposes, include groups such as: NCCIH, Food and Drug Administration, Georgetown University, Georgetown University Institutional Review Board (IRB), and federal research oversight agencies. Please note that administrative personnel

involved in processing your payment for participation may be aware of your identity.

CLINICALTRIALS.GOV

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

DATA SECURITY

If information about your participation in this study is stored in a computer, we will take the following precautions to protect it from unauthorized disclosure, tampering, or damage:

We will make our best effort to keep all data confidential. Alphanumeric codes will be assigned to participants on enrollment. All questionnaires will be identified by this unique code. Research personnel will keep questionnaires and data sheets containing identifiable information in separate locked cabinets or in a password-protected database. No identifiable information will be allowed outside the secure location. All databases will be password protected to ensure that only study personnel can access the data. The secure servers used for this study are maintained at Georgetown University's data center.

WHAT ARE THE COSTS?

Qualified study participants will not have to pay to participate or for study treatments. You or your insurance company will have to pay for any visits to your treating physician. You or your insurance company will be charged for continuing medical care and/or hospitalization that are not a part of the study.

POLICY/PROCEDURES FOR RESEARCH RELATED INJURY

The Policy and Procedure for the Sponsor, NCCIH, are as follows:

The sponsor, NCCIH, will not pay for care necessitated by a research related injury.

The Policy and Procedure for Georgetown University Medical Center are as follows:

Participation in any research study involves some risk of injury. Although we will take precautions to minimize this risk, you might develop medical complications or injuries from participating in this study. If you suffer an injury directly related to your participation in this project, the PI and the research study staff will assist you in obtaining appropriate medical treatment, and provide referrals to other health care facilities, as appropriate. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care will first be sought from your insurer, managed care plan, or other benefits program. You will be responsible for any associated co-payments or deductibles as required by your insurance. If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs.

Georgetown University, the National Institutes of Health (NIH), and the National Center for Complementary and Integrated Health (NCCIH) and/or its affiliated institutions or health care groups, will not provide you with financial compensation or reimbursement for the cost of care provided to treat a research-related injury or for other expenses arising from a research-related injury.

You do not waive any liability rights for personal injury by signing this form.

PAYMENT FOR PARTICIPATION

You *will* be paid for participating in this study. You will receive up to $120 per the following schedule: $20 at

enrollment, $20 after the run-in period, and $20 each on days 7, 14, 21 and 30. You should not expect anyone to pay you for pain, worry, lost income, or non-medical care costs that occur from taking part in this research study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part in or leave the study at any time. If you choose to not take part in or to leave the study, your regular care will not be affected nor will your relations with your physicians, other personnel and the hospital or university. In addition, you will not lose any of the benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or participation in this study.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

By signing this form you do not lose any of your legal rights.

NEW FINDINGS

Throughout the study, we will tell you about new information we receive about treatments that may be appropriate for you, about the experimental treatments under investigation in this study, and any information that may affect your interest in remaining in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, any problems, unexpected physical or psychological discomforts, or if you think that something unusual or unexpected is happening, call Daniel Merenstein, MD at 202-687-2745 or the Project Coordinator, Keisha Herbin Smith, at 202-687-6454. Be sure to inform your physician of your participation in this study.

If you are a participant at Georgetown University and have questions about your rights as a research participant, contact the Georgetown University IRB Office. Direct your questions to:

Institutional Review Board

Address: Georgetown University Medical Center Telephone: (202) 687-1506
3900 Reservoir Road, N.W. SW104 Med-Dent
Washington, D.C. 20057

Withdrawal by investigator, physician, or sponsor

The investigators, physicians or sponsors may stop the study or take you out of the study at any time should they judge that it is in your best interest to do so, if you experience a study-related injury, if you need additional or different medication, or if you do not comply with the study plan. They may remove you from the study for various other administrative and medical reasons. They can do this without your consent.

THINGS TO THINK ABOUT

The choice to let us collect stool samples for future research is up to you. No matter what you decide to do, it will not affect your care or follow-up. If you desire, we will provide you with a summary of your stool analysis results. You will be able to access this data once the study is completed on a password-protected website. We will provide a summary of the names and amounts of the bacterial species that are present in your samples, with brief descriptions of what these microbes are doing. You will be able to see the extent to which antibiotics changed the makeup of your gut microbial community. You may have read or heard about the microbiome in the news before, as scientists believe it is related to many aspects of health. Unfortunately, we still don't know what makes a healthy microbiome, or which types of (or how) foods or medicines change the microbiome.

We will be providing these results for your information only. While you might want to share this information with your physician, you or your physician should not make any medical diagnoses or treatments based on this microbiome data. We hope the information we learn from your participation in this study will help us to better understand these relationships in the future.

If you decide now that your samples can be kept for research, you can change your mind at any time during the study. Just contact us and let us know that you do not want us to use these samples. Then any samples that remain will no longer be used for research and will be destroyed.

In the future, people who do research on your samples may need to know more about your health. Reports will not have your name, address, phone number, or any other information that will let researchers know who you are. They will be identified by unique numbers that do not allow the researcher the ability to identify who the samples were obtained from.

Your samples will be used only for research and will not be sold. The research done with your samples may help to develop new products in the future. You will not profit from any new product developed from research done on these samples. Each proposed project is reviewed by a group of scientists and by a group that protects your rights as a person joining a research study. Once you've answered the instructions below, you will not be asked again about participation in the specific studies using these banked samples.

MAKING YOUR CHOICE

Please read the sentence below and think about your choice. Please check "Yes" or "No" then add your initials and date after you answer. **No matter what you decide to do, it will not affect your care.** If you have any questions, please talk to Dr. Merenstein or the Project Coordinator, or call the Institutional Review Board at 202-687-1506.

I give my permission for my stool samples to be stored for future use by the study investigators. I give authorization for my accompanying health information to be used and disclosed as marked below:

1. I give permission for my stool samples to be kept by the study investigators for future research to learn more about antibiotic-associated diarrhea, antibiotic use and/or probiotics:

☐ YES NO

Initials	Date

2. I give permission for my stool samples to be kept by the study investigators for future research to learn more about other health problems:

☐ YES NO

Initials	Date

JUN 22 2019
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RESEARCHER'S STATEMENT

I have fully explained this study to the subject. As a representative of this study, I have explained the purpose, the procedures, the benefits and risks that are involved in this research study. Any questions that have been raised have been answered to the individual's satisfaction.

Signature of Person Obtaining Consent	Print Name of Person	Date (MM-DD-YYYY)

I, the undersigned, have been informed about this study's purpose, procedures, possible benefits and risks, and I have received a copy of this consent. I have been given the opportunity to ask questions before I sign, and I have been told that I can ask other questions at any time. I voluntarily agree to participate in this study. I am free to withdraw from the study at any time without need to justify my decision. This withdrawal will not in any way affect my future treatment or medical management and I will not lose any benefits to which I am otherwise entitled. I agree to cooperate with Daniel Merenstein, MD and the research staff and to inform them immediately if I experience any unexpected or unusual symptoms.

Signature of Participant	Print Name of Participant	Date (MM-DD-YYYY)

Reviewed by:

Signature of Principal Investigator	Date (MM-DD-YYYY)

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