Official Title: Safety and Outcomes Associated With Continuous Versus Intermittent Infusion Vancomycin in Outpatient Parenteral Antibiotic Therapy: a Prospective, Randomized Trial
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Department of Pharmacy; Department of Internal Medicine, Section of Infectious Diseases

SAFETY AND OUTCOMES ASSOCIATED WITH CONTINUOUS VERSUS INTERMITTENT INFUSION VANCOMYCIN IN OUTPATIENT PARENTERAL ANTIBIOTIC THERAPY: A PROSPECTIVE, RANDOMIZED TRIAL

Informed Consent Form to Participate in Research
John Williamson, PharmD, Principal Investigator

SUMMARY

You are invited to participate in a research study. The purpose of this research is to test the safety and outcomes of continuous infusion vancomycin compared to intermittent infusion vancomycin. You are invited to be in this study because your doctor has determined that you need treatment with vancomycin in the outpatient setting for at least two weeks. Your participation in this research will last for the duration of vancomycin therapy, which is expected to be approximately 2 to 8 weeks. Participation in this study will involve outpatient therapy with vancomycin, regular laboratory monitoring, and follow-up visits in the Infectious Diseases Clinic.

All research studies involve some risks. A risk of therapy with vancomycin is acute kidney injury. The risk of acute kidney injury is not expected to increase if you choose to participate in this study. There is the possibility that you may benefit from participation in this study.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. If you choose not to participate in this study, you will receive intermittent infusion vancomycin, as prescribed by your doctor. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is John Williamson, PharmD *(Principal Investigator)*. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his contact information is: [redacted].

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted] or the Research Subject Advocate at Wake Forest at [redacted].

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have an infection that requires long-term outpatient treatment with vancomycin. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to compare the safety and effectiveness of continuous infusion vancomycin with intermittent infusion vancomycin. The primary objective of this study is to evaluate if continuous infusion vancomycin is safer for kidneys.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Two-hundred people will take part in this study at Wake Forest Baptist Health.

WHAT IS INVOLVED IN THE STUDY?

You will be randomized into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have an equal chance of being placed in either group.

You will receive vancomycin in the outpatient setting as treatment for your condition for at least 2 weeks. This has already been determined by your doctor. You will be randomized to receive vancomycin as a continuous infusion (24-hour infusion) or intermittent infusions (shorter infusions scheduled 2-3 times per day). You will be trained on how to self-administer doses of vancomycin irrespective of which infusion type you receive. Regardless of the group you are assigned, you will receive the same amount of vancomycin.

There are many facets of standard care provided in the Infectious Diseases Clinic for patients receiving vancomycin, regardless of your participation in this study. The following describes parts of this care you will receive regardless of which group you are assigned: follow-up visits at the Infectious Diseases Clinic, home health visits, telephone calls, laboratory tests, and x-rays or other scans. Your doctor or pharmacist will determine what visits are needed, and what tests need to be performed. Continuous infusion is not expected to result in more or less laboratory tests than receiving multiple shorter infusions. No extra laboratory tests will be performed because of your participation in this study. Treatment with vancomycin will be continued until your doctor tells you to stop taking it.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study until your doctor decides to stop vancomycin, either approximately 2 – 8 weeks or if a safety event occurs. You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn

about any potential health or safety consequences. If you stop participating in the study, your doctor may continue therapy with vancomycin, but possibly with different infusion.

WHAT ARE THE RISKS OF THE STUDY?

Your doctor has decided to treat you with vancomycin. It is uncertain whether the type of infusion effects your chance of having a side effect. Small studies have not identified an increased chance in experiencing a side effect if given continuous infusion. You should discuss the risk of being in this study with the study staff. Risks and side effects related to vancomycin (given by continuous infusion or intermittent infusion) include:

- Kidney injury
    - ~5% of patients
    - This is usually reversible
    - The risk is increased with age and in combination with other medications known to harm the kidney.
- Allergic reactions:
    - This is reversible
    - Flushing, hives, rash
- "Red Man Syndrome": flushing, swelling, or rash on the face, neck, chest or upper extremities. Low blood pressure may occur, as well.
    - Uncommon
    - When it does occur, this will typically happen during the beginning or end of the infusion.
    - This is reversible and prevented by slowing down the rate of the infusion.
- Nausea
    - Uncommon
- Low white blood cell count
    - Uncommon
    - This is reversible upon discontinuation of therapy
- Low platelet count
    - Uncommon
    - This is reversible upon discontinuation of therapy.
- Hearing toxicity
    - Rare and may be temporary or permanent.
    - This is associated with high peak levels that are not seen in modern dosing of vancomycin.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other risks that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep

your information safe.

During blood draws for vancomycin monitoring:
No matter which infusion of vancomycin you receive, blood draws for vancomycin levels will be performed. The amount of blood required to monitor vancomycin will be determined by the number of lab tests ordered by your doctor. No extra blood draws will be performed because of your participation in this research. You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy lightheaded or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. A possible benefit of participating in this study is reduced risk of kidney injury as a side effect of vancomycin. Because individuals respond differently to therapy, no one can know in advance if it will be helpful in your particular case.

Based on what is known about continuous infusion vancomycin, the chance of success in treating your infection is not expected to be any different than intermittent infusion vancomycin.

WHAT OTHER CHOICES ARE THERE?
You do not have to be in this study to receive treatment. If you choose not to participate in this study, you will receive intermittent infusions of vancomycin. You should talk to your doctor about all the choices you have.

WHAT ARE THE COSTS?
As your doctor has determined that treatment with vancomycin is necessary, there is no additional cost for participating in this study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

You or your insurance company will be billed for home infusion services including medications and devices related to vancomycin administration. The cost of continuous infusion vancomycin will be equal to the cost of intermittent infusion vancomycin, because the amount and duration of vancomycin treatment will be the same regardless of the type of infusion. If your insurance company is billed, they will determine your out of pocket cost for therapy.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?
The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required.

The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

WILL YOU BE PAID FOR PARTICIPATING?

You will receive no payment or other compensation for taking part in this study.

WHO IS SPONSORING THIS STUDY?

This study is being conducted by the Wake Forest Baptist Health and there is no external sponsor involved.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Wake Forest Baptist Health will not reimburse for medical expenses incurred by research subjects for medical care, including hospitalization, in the treatment of adverse reactions arising from study drugs, devices, intervention, procedures and tests following their administration or use in accordance with the protocol, which expenses were not caused by negligence or misconduct of any person in the employment of Wake Forest University Health Sciences or to your own failure to follow instructions. Wake Forest Baptist Health is not responsible for expenses that are due to pre-existing medical conditions or underlying disease.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call John Williamson, PharmD at [redacted]

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** age, weight, list of medical problems/diagnoses, progress notes, home medications, laboratory values (complete blood cell count, basic metabolic panels, etc.), vancomycin dose, vancomycin levels, and interpretation of imaging studies (x-ray, CT scan, MRI, etc.).

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, and to provide required reports.

Some of the people that may receive and use your health information are the research personnel, the Institutional Review Board, representatives from government agencies such as the Food and

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Drug Administration (FDA) or the Office of Human Research Protections (OHRP), and the Department of Health and Human Services (DHHS).

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to the participant's original medical record for verification of clinical trial procedures or data, without violating confidentiality of the participant and to the extent permitted by other applicable laws.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least one year after the study is finished. At that time any research information not already in your medical record will either be destroyed or it will be de-identified. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell John Williamson, PharmD that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

John Williamson, PharmD
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people

who have authorized access to your medical record.

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 Web site at any time.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because of one of the following: it is in your best medical interest, your condition worsened, new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped. Information that identifies you may be removed from the data and could be used for future research or shared with others without additional consent.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, John Williamson at [redacted]. If calling after business hours, please leave a message and a call will be returned during the next business day.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted] or the Research Subject Advocate at [redacted].

You will be given a copy of this signed consent form.

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SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____ Date:_____Time:_____am pm

Legally Authorized Representative Name (Print):_____

The above named Legally Authorized Representative has legal authority to act for the research subject based upon (specify health care power of attorney, spouse, parent, etc.)

Relationship to the Subject:_____

Legal Representative Signature:_____Date:_____Time:_____am pm