Antibiotics for cellulitis; 6 or 12 days?

Dear sir/madam,

We would like to ask you to help us with a scientific study that intends to answer the medical question in the title. This study is being performed in eleven hospitals in the "Randstad" region, and will include almost 316 patients. You alone can decide if you want to participate. Before making a decision, please allow us to tell you more about the study. Read this information folder carefully, and/or discuss it with a partner, friend or family member. You can also call an independent doctor, who knows a lot about this study. There is also a general information folder on medical research, written by the Dutch government, which answers a lot of general questions. Do you still have questions after reading all this information? You can always ask the investigator of this study. You can find his contact details at the bottom of this folder.

1. What is the purpose of this research / study?

Cellulitis is an infection of the skin, caused by bacteria. It is a very common disease, for which people are often admitted to the hospital. It is treated with antibiotics, which kill the bacteria. It is unclear whether the standard course of 12 days of antibiotics that patients currently get, is the right duration, or if it is maybe too long. In other infections (like pneumonia or bladder infections), research has recently shown that a short course of antibiotics works just as well. A short course is preferred, because:

* Patients will need less antibiotics, so have fewer (or shorter lasting) side effects
* Costs would be lower
* Bacteria will be less likely to develop resistance, which would make them immune to antibiotics (which would mean antibiotics would no longer kill these bacteria)

This is why we want to investigate if a short course of 6 days of antibiotics, works just as well as a standard course of 12 days. We also want to investigate what the underlying mechanisms of this disease are, so we can possibly predict who should and who shouldn't be admitted to the hospital for treatment.

2. Which treatment is being studied?

In this study, we compare the standard antibiotics (flucloxacillin, also known as Floxapen) with a duration of 12 days, to 6 days. In short: we're comparing the standard therapy to a shorter therapy.

3. How is this study being performed?

Every participant begins with admission to the hospital, and receives IV antibiotics. After admission, we'll come to visit you, usually within the first 24 hours, otherwise within 72 hours. On the 5th or 6th day (counting from the moment of admission) we'll come evaluate your condition. If your symptoms have improved, it's a sign that the antibiotics are working.

At that time, we think all the bacteria are dead, and all remaining symptoms are simply leftover inflammation, which is the reaction of the body to an infection. Given enough time, this inflammation will decrease by itself without needing antibiotics. If the symptoms haven't improved, it might mean the antibiotics haven't worked, and we could no longer continue your participation in the study.

If your symptoms have improved, you would be "randomized", which means you would be assigned to one of two groups. Both groups get 6 days of antibiotics, counting from the time of admission. One group will get 6 more days of antibiotics after that, giving them 12 days total (the current standard therapy). The other group will get 6 days of placebo, which is a pill that looks like antibiotics, but doesn't contain any. This group will have a total of 6 days of antibiotics (the shorter therapy).

The study is blinded, meaning no one knows what's in your medication, except for the pharmacy (so not you, not us, not the nurses, and not the doctors on the ward). This leads to more reliable study data. The total treatment lasts for 12 days for everyone. We will visit you again on the 14th and 28th day to measure the effect of the therapy. You will likely be discharged early on. The researchers can make appointments with you for these follow-up visits. He or she can come to your house so you won't need to come to the hospital, although sometimes it's possible to come to the hospital outpatient clinic. Travel expenses will be reimbursed. On the 90th day, a few last questions will be asked during a telephone call.

4. What is expected of you?

During the study you are treated as a regular hospital patient. All your other medication can be used like you would otherwise. You don't have to abide by any special rules. The only difference is the medication you will get after the sixth day. You will get the capsules (with either antibiotics or placebo) four times per day, as you would during regular care. It might be that you get the capsules three times per day, if your kidney function is below a certain level, which is also standard care. The researcher will inform you of this, if this is the case.

5. What is different from the regular treatment?

Normally, people are treated with antibiotics for 12 days. In this study, ~50% of the patients will get that standard treatment. The other half gets 6 days of antibiotics and 6 days of placebo (which is not an antibiotic), instead. At five points in time, we will draw extra blood (between 10 and 36 ml each time), and we will ask you to fill in questionnaires. We will swab your skin on two days with cotton swabs. We will also take pictures of the infection and the opposing limb, to document the progress of the disease. You will not be recognizable, meaning your face will not be in the picture.

6. What are the other possible treatment options?

Within this study, we only look at flucloxacillin, which is the recommended antibiotic for this disease in the Netherlands. If you are allergic to flucloxacillin, or the agent appears to be ineffective, you will get another antibiotic (which is also according to recommendations), but you will be unable to participate in this study.

7. Which side effects are to be expected?

Flucloxacillin has been used many years and the side effects are well known. Even if you don't participate in our study, you might develop these side effects. The most important are diarrhea, nausea, vomiting and a skin rash.

8. What are possible (dis)advantages of participating in this study?

If you are in the placebo group, you might have less (or shorter lasting) side effects of flucloxacillin. There are no other advantages for you specifically, when you participate. However, future patients with the same disease can benefit from the results of this study.

Disadvantages of participating are:
- there is a small chance that 6 days of treatment is less effective than 12 days of treatment, in which case you would still be able to get the standard treatment
- during and after the disease period, we will ask you to take some time to fill in questionnaires (see appendix 2)
- there will be five extra blood draws during the study period. This is a small amount, between 10 and 36 ml each time, and will not affect your health. As a frame of reference; an adult has somewhere between 4000 and 6000 ml of blood in his/her body.

9. What happens when you don't participate in this study?

You decide whether you want to participate or not; it is completely on a voluntary basis. If you decide not to participate, you don't need to do or sign anything. You also don't need to tell us why you won't participate. As a patient, you will still get the standard care. If you decide to participate, you are always free to change your mind and quit, even during the study.

10. What happens when the study is finished?

The study is finished after 90 days. If you decide to quit earlier, or if we think it is medically necessary to remove you from the study for your own benefit, the study can be finished before that. When that happens, you'll be treated as we would any other patient. Quitting has no disadvantages for you whatsoever.

11. Are you insured when you participate in this study?

We have an insurance for all patients who participate in this study. This insurance covers damages that are inflicted as a result of this study. This applies to damages which become apparent during the study, or within four years after the study is finished. In appendix 1 you can find the insured amounts, the exceptions, and the address details of the insurance agent and contact person.

12. Will you be informed of newly discovered information that might be relevant to you?

The study will follow its protocol as strictly as possible. But the situation can change, f.e. due to a reaction of your body against the study drug, or due to other new information. If that is the case, we'll discuss it with you right away. You can decide at that time if you want to continue with the study or quit. If your safety or health is in danger, we will take you out of the study immediately.

13. What happens to your data?

Your data are being stored in coded form, under a study ID number instead of your name. Only the investigators have the key to this coding list. However, also the national Health Care Inspectorate, or people assigned by the AMC to monitor the course of the study, can review your information, for safety reasons. We are obliged by law to store your data for 15 years. If you participate, you agree to these terms. If you don't want that, you unfortunately can't participate in this study.

14. What happens to your bodily materials?

With your bodily materials we want to do multiple other investigations. These investigations are meant to provide insight into how the body fights off the infection, and how other processes (like coagulation) are affected by the infection. We are also looking for ways to determine which infections will be more severe than others, by looking at blood markers, or by skin swabs. When doctors have more knowledge on how diseases start out, it is easier for them to develop better treatments.

Sometimes results from investigations can be important for your own health. This is the case for things like risks to get diseases, which can be reduced with early medical intervention. Or the discovery of a disease you already have that requires treatment. The chances of discovering things like this is very small. However, if we do find such a thing, we will inform you and your attending physician of this. With your permission, we will also inform your general practitioner (GP, house doctor). If you do not want to be informed of these kinds of results, you can't participate in the study.

Your bodily materials can also be important for later research into this disease. That's why we would like to store the left-over materials after this study, for another maximum of 15 years, for use in research on cellulitis. It will only be accessible to AMC investigators, and they will not be able to see who the materials belonged to, because it is coded with a study patient ID, and not your name, date of birth, or hospital patient ID. If you do not want that, we will respect your decision. You can write this on your informed consent form. You can also come back on this decision at a later time, we will then destroy your materials at that time. More info on this can be found in the general information folder on medical research.

Is your GP/house doctor, and/or your attending physician informed of participation?
We will send your GP/house doctor a letter to inform him of your participation. This is for your own safety. Your attending physician will also be informed.

16. Are there extra costs, or is there a compensation for participating?
No, there is no compensation for participating. Travel expenses for visits are refunded.

17. Which medical ethical board has approved this study?
The medical ethical review board of the AMC (Amsterdam) has approved this study. More information on such approval can be found in the general information folder.

18. Do you still have more questions?
You can always contact the investigators for questions (contact details below). Would you rather get independent advice on participating with this study? You can find the contact details of an independent expert (infectious diseases specialist) below. You can also find the contact details of the complaint committee below.

19. Appendices
- General information folder on medical research
- Table with study procedures per day
- Insurance text
- Local information

20. Contact details

Investigator (**primary contact person for questions)**	Mr. D.R. Cranendonk, MD d.r.cranendonk@amc.uva.nl Tel: 020-5665247
Study leader / coordinator	Mr. W.J. Wiersinga, MD, PhD internist-infectiologist w.j.wiersinga@amc.uva.nl
Institution	Academic Medical Center (AMC)
Department	Center for Experimental and Molecular Medicine (CEMM) Tel: 020-5665910 (secretariat)
Address	Room G2-130, Meibergdreef 9, 1105 AZ, Amsterdam
Independent expert for questions	Mr. J.W.R. Hovius, MD, PhD internist-infectiologist j.w.hovius@amc.uva.nl Tel: 020-5666309

Appendix 1. Insurance information

In accordance with the Medical Research (Human Subjects) Act, the sponsor has taken out an insurance policy for medical research that covers damages caused by death or injury of test subjects of this study.
* This pertains to damages that manifest themselves while participating in the study or up to four years thereafter, and that are reported four years after termination of participation in the study.
* The amount of coverage provided by the insurance is €450,000.00 per subject, with a maximum of €3,500,000.00 for the entire study and €5,000,000.00 for damages caused by medical research that is reported for each insurance year.

The insurance covers:
* against damages resulting from the manifestation of risks associated with participating in scientific research, about which one was not informed in writing;
* against damages resulting from the manifestation of risks about which the participant was in fact informed, but that were more severe than anticipated;
* against damages resulting from the manifestation of risks about which the participant was informed, but that were considered highly unlikely.

The insurance does not cover:
damages that result from health problems of the test subject not being reduced, or that result from a further deterioration of medical problems, if participation in the scientific research occurs as part of the treatment of those health problems;

* damages caused by harmful effects on the health of the test subject if it is likely that they would have occurred anyway even if the test subject had not participated in the study;
* damages resulting from participating in medical research in which the medical procedures standardly employed by experts in the field are compared with each other and it is likely that the damages are the result of the employed procedures;
* damages that appear in the offspring of the test person as a result of a side effect of the study on the test subject or his offspring;
* damages resulting from the test subject entirely or partially not following the instructions and directions, at least if the test subject was in fact able to do so.

The insurance covers only damages to natural persons. The coverage of specific damages and costs is limited to certain amounts.
In the event of alleged damages as a result of the study, to be able to claim damages the test subject must report them to:

Name/address of the insurance company:
Centramed B.A.
Postbus 191
2270 AD Voorburg
Policy number: 43NE032039

The test subject is also asked to contact dr. W.J. Wiersinga (tel.: 020-5661109) in connection with this issue.

Appendix 2. Table with study procedures per day

When: / Procedure:	Day 1	Day 2-3	Day 5-6	Day 14	Day 28	Day 90
Give informed consent	X					
Physical examination (if attending physician hasn't already performed it)	X		X	X	X	
Drawing blood samples	X	X	X	X	X	
Skin swabs	X			X		
"Cellulitis score" as measure of inflammation	X	X	X	X	X	
Scoring your current health status	X	X	X	X	X	X
SF-36 and EQ-5D questionnaires	X				X	X
Questionnaires on health care resource utilisation			X		X	X

Appendix 3. Local information

Committee for complaints, AMC Postbus 2260, 1100 DD Amsterdam

Tel: 020-566-4094; ckb@amc.nl

Informed consent form

Antibiotics for cellulitis: 6 or 12 days?

I have read the information folder for study participants. I was able to ask additional questions. All my questions have been answered. I had enough time to decide if I wanted to participate.

I know participation is on voluntary basis. I know I can decide at any time to quit, without having to provide a reason why.

I know that some people are able to see my information. Those people are the study team, people appointed by the AMC for monitoring or auditing purposes, or representatives of the Health Care Inspectorate, as mentioned in the information folder.

I give permission to use my information and data, for the purposes listed in the information folder.

I give permission to store my information and data for 15 years after the study has finished.

I give permission to inform my general practitioner / house doctor of my participation in this study.

I will allow pictures to be taken of my infection. These *can / can not** be used in publications in scientific journals, provided I am not recognizable.

I voluntarily donate my bodily materials (blood) for research purposes.

I *give / do not give** permission to store my bodily materials for 15 years after the study has finished, so that in the future it might be used for research as described in the information folder.

* : strike through as applicable

I want to participate in this study.

Name of participant:

Signature: Date: ___ / ___ / _____ (dd/mm/yyyy)

I hereby declare that I have informed this participant completely about the contents of the study.

If during the study, information arises which might alter the way the participant feels about participating, I will inform him/her of this in a timely manner.

Name of investigator (or representative):

Signature: Date: ___ / ___ / _____ (dd/mm/yyyy)

Additional information is given by (if applicable):
Name:
Function:

Signature: Date: ___ / ___ / _____ (dd/mm/yyyy)
