

# Outbreak of *Nocardia* Infections in Heart Transplant Recipients and Association with Climate Conditions, Australia

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Nila Dharan, an infectious disease physician at the University of New South Wales in Australia. We'll be discussing an outbreak of *Nocardia* infections in heart transplant recipients and association with climate conditions in Australia.

Welcome, Dr. Dharan.

[Nila Dharan] Thank you very much and thank you for the invitation.

[Sarah Gregory] What is *Nocardia*?

[Nila Dharan] So *Nocardia* is a bacteria that's commonly found in the environment. It belongs to the family *Actinomycete*, and stains positive on Gram stains. And that's often how it's first diagnosed—is on a Gram stain taken from the patient, which is a stain of a patient's sample. *Nocardia* is generally found in soil and water, and it's generally acquired as an infection through inhalation. Once it's inhaled, it starts to cause a pulmonary infection. From this pulmonary infection, it can often go into the bloodstream and go to other parts of the body. The other way you can acquire *Nocardia* is through direct inoculation into the skin—so, that's if you get pricked by a rose thorn or scratched by a tree branch and the *Nocardia* bacteria is on that, you can get a local skin infection there.

Now, skin infections are most commonly reported in immunocompetent people (so, people with normal immune systems). But when you get people (such as transplant recipients, in this case) who have compromised immune systems because they're taking medications that lower their immunity, they often times get more serious infections—so, very serious pneumonias, and again, that disseminated or widespread illness that I described before where they can get spread through the bloodstream into places like their bones and even into the brain.

[Sarah Gregory] So soil and digging in your garden and walking by construction sites...can you get it those ways?

[Nila Dharan] You can. It's most commonly acquired, again, as I said, through inhalation of soil that has the bacteria in it. And so, when patients are immunocompromised, they are often advised to avoid gardening or avoid things that expose them to soil and water because their immune system is not as strong as it needs to be, and they are also advised if they are going to be exposed to those types of things, to wear the appropriate personal protective equipment (or PPE), such as masks and gloves.

[Sarah Gregory] Where did the outbreak occur that you investigated?

[Nila Dharan] So this outbreak occurred in the greater Sydney area in New South Wales. We worked at a hospital called St. Vincent's Hospital in Sydney, and we noted an increased rate of *Nocardia* infections among our heart transplant recipients there. These heart transplant recipients don't all live exactly in Sydney. The majority of them do, but many of them live in the greater Sydney area, meaning several hours outside of Sydney.

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[Sarah Gregory] Why did you do this study?

[Nila Dharan] We did this study because we noticed that we were seeing an increased rate of *Nocardia* infections in heart transplant recipients at St. Vincent's Hospital. And the interesting thing with that, we could not see the same increase among lung transplant recipients who were operated on and treated at the same hospital. So what we wanted to do was, first of all, compare differences between the heart transplant recipients and lung transplant recipients in order to understand why there was a difference in these two patient groups. And the second thing we wanted to understand is why we saw this rise in *Nocardia* infections. We did note that the rise in infections coincided with a period of very extreme weather conditions in New South Wales, which is the state that Sydney is in; 2018, when we saw the outbreak start, and 2019, where we saw the increase go through 2019, we found that those two years were some of the warmest and driest on record (actually, 2019 was the warmest and driest year on record in New South Wales).

So we were interested in trying to understand whether or not the increased number of cases of *Nocardia* infections was related to climate conditions (or at least correlated with climate conditions), and also to understand why heart transplant recipients were having more infections than the lung transplant recipients.

[Sarah Gregory] So you looked at the time period of 2018 and '19 because you were seeing an increase in cases then, is that right?

[Nila Dharan] Yes. So that was the period of the outbreak, was from early 2018 to the end of 2019. And we saw the subsiding of cases after that back to baseline levels. We then wanted to look at before and after the outbreak to compare those time periods. So we went all the way back to June of 2015, which is when we had data from our microbiology lab available. So then we had a pre-outbreak period from June 2015 to January 2018, the outbreak period of 2018 and 2019, and then we looked post-outbreak from January 2020 to March of 2021. And again, this is to compare before, during, and after the outbreak.

[Sarah Gregory] You mentioned differences between heart transplant recipients and lung transplant recipients. Could you tell us some more about that?

[Nila Dharan] Yes. So what we found when we looked at their clinical information was that the heart transplant recipients who got *Nocardia* had more characteristics indicating a greater level of immunosuppression than lung transplant recipients, meaning that their immune systems were not as strong potentially compared with the lung transplant recipients, and this may have made them more likely to be susceptible to *Nocardia* infection. So some of these characteristics included a higher rate of a use of a specific agent called basiliximab for induction immunosuppression right prior to transplant. This immunosuppressant has some effects that decrease some of the immune system cells that you have, and we think that this compromises these immune system cells may have increased the risk for *Nocardia* infection in these patients.

The other thing we found is that heart transplant recipients had more diabetes (which is immunocompromising), and also more episodes of transplanted organ rejection. Now, when you see organ rejection, the treatment is to increase your immunosuppression, and we found that they not only had more episodes of all types of organ rejection, but also more episodes of treated moderate-to-severe rejection. So again, these treated episodes of rejection usually include additional immunosuppression, and we think this may have further increased their risk of acquiring *Nocardia*.

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[Sarah Gregory] Was the treatment different for these two groups and what is the treatment?

[Nila Dharan] So the treatment for *Nocardia* varies quite a bit, depending on whether or not your patient is immunocompetent or immunocompromised and also how extensive the disease is. So the most mild form of skin infection, for example, in immunocompetent infection requires a single antibiotic, which you take orally for three months. With the most severe form which you might see in immunocompromised individuals more commonly such as disseminated disease, very severe pneumonia, and brain abscesses, this involves treating with multiple oral antibiotics and often times even intravenous antibiotics to start. And the treatment can be up to 12 months and possibly even longer, depending on the situation of your patient.

[Sarah Gregory] What are the demographics of the patients—age? Gender?

[Nila Dharan] So we identified a total of 23 cases of *Nocardia* in both heart and lung transplant recipients during June 2015 to March 2021; 16 were heart transplant recipients and seven were lung transplant recipients. So the median age at the diagnosis of *Nocardia* was 59, and the youngest patient was 38 and the oldest was 71, and we found that 65% of the patients were male.

[Sarah Gregory] How did you conduct this study?

[Nila Dharan] So what we first did is we identified all *Nocardia* cases based on those identified in our microbiology lab that belonged to a heart transplant patient or a lung transplant patient, and again, from June 2015 to March 2021. We then went back and looked at the medical records of these patients, and we looked for their date of transplant, the date of *Nocardia* diagnosis, which *Nocardia* species were identified, what the site of infection was, whether or not they had been on any antibiotics prior to their diagnosis, whether or not they had any diagnosis of any other infections, and what their induction and maintenance immunosuppression regimens had been. We also looked at other things around their transplant, such as the donor and recipient CMV status and organ rejection rates, as I mentioned earlier. We then looked at where these patients lived and tried to see if any of them were clustered in location or clustered in time. And then, we also used their location to correlate with climate data to see if there were climate factors that influenced development of *Nocardia*.

[Sarah Gregory] Where did you get the climate data that you used?

[Nila Dharan] We obtained our meteorological data from our colleagues at the Centre of Excellence for Climate Exchange and Climate Change Research at UNSW in Sydney, and this meteorological data comes from the European Centre for Medium-Range Weather Forecasts Analysis (or ERA5). And we got this data for each suburb in which our *Nocardia* patients resided. Now, ERA5 is a system that's based on the Integrated Forecasting System (a global numerical weather prediction system), and the ERA5 reanalysis give us a set of consistent daily data from 1950 to the present and has a resolution of 31 kilometers. We used this data to define various characteristics of data; we looked at temperature and rainfall and we also looked at dryness, and dryness is calculated as a ratio of actual evaporation to potential evaporation, and it reflects the moisture content of the surface.

[Sarah Gregory] Okay, so you have this data. How did climate actually play into this outbreak?

[Nila Dharan] It was very interesting. So we found that in the area of our *Nocardia* cases, the increase in cases occurred during times of decreased rainfall and during times of having a very dry surface. So again, dryness was defined as evaporation over potential evaporation. And this

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supported our hypothesis that we found that the increase in *Nocardia* infections we saw might have been driven by climate conditions. So again, 2019 was the warmest and driest year in New South Wales on record, and we had an average mean temperature of almost two degrees centigrade above the average and an average rainfall 55% below average. And 2018 was New South Wales second warmest and seventh driest year, with an annual temperature of about two degrees above average and annual rainfall 40% below average.

[Sarah Gregory] Was a single source of infection ever identified?

[Nila Dharan] No, we did not. So we didn't find any single species of *Nocardia* that was identified. There were multiple species indicating that there were multiple different forms of *Nocardia* that were causing these infections. And also, there was a very broad range in time from transplant to diagnosis. And also, when we looked at those cases that were clustered together geographically, they were actually diagnosed very far apart. Most cases were diagnosed more than six months apart from each other, and again, with different species. So this indicates that there was not a single source of this outbreak.

[Sarah Gregory] And after all this investigation, what did you conclude?

[Nila Dharan] So what we concluded is that we think that the increased environmental risk from climate conditions coupled with increased host susceptibility related to immunosuppression in heart transplants likely explains the increased incidence of *Nocardia* that we found during 2018 to 2019.

[Sarah Gregory] Were there any challenges, and if so, what were they?

[Nila Dharan] There were two main challenges. The first challenge is just that we have a small study population size, and this is just reflective of the fact that *Nocardia* is quite uncommon. And so, even when you have a *Nocardia* outbreak, it's not like you have hundreds and hundreds of cases. So this did limit some of our analyses and kept our statistical analysis to just descriptive statistics and correlations with climate data. We also had this retrospective study design, and so we were relying from data that we could obtain from the medical records. And it also limited our ability to comment on any patient practices, such as whether or not they were using personal protective equipment or exposing themselves in any activities, such as gardening. We also didn't...again, because it was retrospective, we didn't have any data on intraoperative care, such as changes in procedures or personnel or infection control. However, we don't think that any (at that time) changes in these types of practices were likely to have occurred or likely to be responsible for having an increased risk of *Nocardia*.

[Sarah Gregory] Were you surprised by anything?

[Nila Dharan] We were surprised, actually, to find the correlation with climate. I think...it has been shown in several other studies looking at other infections, but I think just because we had small numbers and we weren't sure exactly whether or not the geographic variability would be great enough to show that there were differences in geographic location and increased risk. But it was very interesting to see that this correlated. And again, it has been shown in other infections that are acquired through the soil, such as *Aspergillus* and *Coccidioides*. So it was a pleasant surprise, but I was a bit surprised to see such a strong correlation with the climate.

[Sarah Gregory] What are the public health implications of your study?

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[Nila Dharan] In terms of public health, I guess everybody's very focused on climate and climate changes, and I think the important thing here to remember is that when you're dealing with very immunosuppressed patients who are at risk for getting infections, you want to protect them as much as possible. And I think the most important message is, of course, that you use personal protective equipment and to avoid any activities that may increase your risk of acquiring infections. And potentially, with our findings and with some of the other findings that are coming out in the literature with correlations with climate, this would particularly apply to patients who are living in very dry areas or areas that there is little rainfall, and certainly to patients in areas where they are having extreme climate conditions.

[Sarah Gregory] Are there any next steps or future studies that you suggest?

[Nila Dharan] Well, certainly I think looking more at data and risk of infection in immunocompromised individuals (and even in immunocompetent individuals) is very important, particularly as we all are watching weather patterns and trends in the global climate situation. So I think certainly more studies in this and more studies in looking at the risk factors for acquiring infection as related to either activities or climate or environment. This will help us understand the risk factors and may even give us some potential screening or added preventive measures that might decrease the risk of these infections in patients.

[Sarah Gregory] Given the global climate situation, do you think we'll see more increases of this kind of infection?

[Nila Dharan] Not being a climate expert myself, I think it's hard for me to predict whether or not we will see more infections of this kind. However, I do think that if trends continue and we do have less rainfall or higher dryness on the surface, this may increase the risk of people getting these kinds of infections. I think the important thing to remember is that it's important to watch these types of climate changes and also record these infections in our patients so that it can be reported, and other people (other physicians in other climates) who may be seeing differences in types of infections their patients are getting can then pay attention and also look to the climate data.

[Sarah Gregory] Let's go back over how people can protect themselves.

[Nila Dharan] So anyone who's immunosuppressed should receive information from their doctors about, first of all, what activities to avoid; and secondly, what sort of personal protective equipment to use if they are to engage in those activities and for other reasons. And so, certainly for gardening, we recommend that patients wear masks, and we recommend that they use gloves. We recommend that they are very careful with the masks that they use, not to scratch their faces or pull them down—certainly all the things that we've talked about with COVID-19 about mask use and doing good masking. I think the important thing to remember is that patients also have to have a quality of life. And so, if you have a patient who's an avid gardener and not gardening is going to be very detrimental to their quality of life, again, it's all about education—making sure they understand the risks, how to avoid those risks or reduce those risks, and how best to protect themselves.

[Sarah Gregory] Dr. Dharan, tell us about your job and what you most enjoy about it.

[Nila Dharan] I'm a clinician scientist, so I really have two jobs and they're very closely related. So first I'm an infectious diseases doctor. I love being an infectious diseases doctor, it's quite

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challenging and quite varied. We manage illness in all parts of the body and from all types of organisms, and often times we get to play the role of disease detective because we're referred patients where other general practitioners or other services haven't been able to make a diagnosis. And we also manage infections that are both chronic and incurable, and those that are acute and curable. So there's a wide range of types of things you see, the types of patients you see. And also, we see a lot of vulnerable patients, so patients who are immunocompromised, like the ones I have been talking about and intravenous drug users and patients with HIV, hepatitis C. So it's quite a rewarding field and quite a challenging field. And I think what I love most about being a doctor is that you can help people manage these infections and improve their quality of life so that they can get on with enjoying their lives as much as possible. My second job is a scientist or a researcher. I love being able to identify challenging questions and designing a research project to answer those questions. I also really enjoy writing and disseminating the findings through publication or a presentation at conferences.

And I think this study was a very nice example of where these two things overlap quite closely. So in my clinical practice (seeing heart transplant patients at St. Vincent's hospital), we identified this problem. It then led to us designing a study to answer the questions, which were why was this happening in heart transplant patients and not lung transplant patients, and why over time was this happening and was it related to the extreme weather conditions in 2018 to 2019? And in the end, we've answered this question and written the publication, and so now we're disseminating the results so that others can benefit from this knowledge. It's a very busy couple of jobs; very challenging but also incredibly satisfying.

[Sarah Gregory] Well, thank you so much for taking the time out of what is clearly a very busy life to talk with us today.

[Nila Dharan] Thank you very much, Sarah. It has been my pleasure.

[Sarah Gregory] And thanks for joining me out there. You can read the November 2022 article, Multispecies Outbreak of *Nocardia* Infections in Heart Transplant Recipients and Association with Climate Conditions, Australia, online at [cdc.gov/eid](https://www.cdc.gov/eid).

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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