

Discovering and researching a pneumocystis pneumonia outbreak among renal transplant patients

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Pneumocystis jirovecii is a fungal infection that causes pneumonia, often in highly immunocompromised patients, such as those recently

undergoing transplants. Before 2019, Marwan Azar, MD, FAST, and his colleagues in Internal Medicine and the Section of Infectious Diseases had not witnessed an outbreak of *Pneumocystis pneumonia* at Yale New Haven Hospital (YNHH). Despite genetically confirmed outbreaks in many areas, including Canada, Europe, and Japan, there had never been such a case in the United States.

However, come 2019, physicians within the [transplant](#) and infectious disease service at YNHH started noticing anecdotally that they were seeing many cases of *Pneumocystis pneumonia* among their kidney transplant patients. Azar noted that "between 2012 and 2018, a six-year period, we had only four cases of *Pneumocystis* within kidney transplant patients. And then suddenly, in May 2019, we started seeing an uptick anecdotally—we saw around 19 cases of *Pneumocystis*. So obviously, as clinicians, we knew something was wrong."

They realized that they may have an outbreak on their hands. After six or seven patients had tested for [pneumocystis](#), they put together an ad hoc committee for an epidemiological investigation, starting with the case definition. Basically, what are the suspected cases? For Azar and his colleagues, the suspected cases included anyone with suspected *Pneumocystis* who was a renal transplant recipient.

"We noticed when recording the number of clinic visits, that the people who had more visits tended to have an [increased risk](#) of getting *Pneumocystis*," said Azar. This led to the second part of the investigation, a case-control study, where they compared patients who had *Pneumocystis* with patients who were the same age and year of transplant who did not have *Pneumocystis*, and compared [risk factors](#), such as age, belatacept (an immunosuppressant for [kidney transplant patients](#) that requires monthly infusions within the transplant clinic), race and type of induction therapy, from there. What they found was that "belatacept was a risk factor, but what was even more of a risk factor

was the number of clinic visits. We found that people who were on belatacept had more clinic visits, because they had to get the infusion. So maybe belatacept is just a proxy, for another more independent risk factor."

The final part of the study was the genetic investigation. Yale physicians collaborated with the National Institutes of Health (NIH), who performed next-generation genetic sequencing, sequencing the entire genome of pneumocystis.

Overall, they collected around nine successfully amplified specimens. Azar remarked, "We were really stunned to find that instead of having one genetic outbreak strain, that had been described in literature before, there were multiple clusters at the same time. So, it seemed like it wasn't just one strain of Pneumocystis that was transmitted, but multiple." What was remarkable was that not only were there multiple strains, but patients were co-infected with multiple Pneumocystis strains at the same time. Almost unbelievably, there was one patient that was infected with seven different strains.

Following their discussion, the clinicians presented the information from the study to the Transplant Nephrology QAPI. They came to the decision to put together a commission where they would identify all patients with low absolute lymphocyte count and start them prospectively on prophylaxis to block ongoing transmission. They're also in contact about infection prevention with Richard A. Martinello, MD, and Scott Roberts, MD, MSCI, who specialize in infectious disease transmission about evaluating ventilation systems within the transplant clinic.

Compared to past studies which did not perform [next-generation sequencing](#) and likely limited their comparison to certain sets of genes, Azar believes that "one major takeaway is that next-generation sequencing should be considered a potential, critical tool in future

outbreak investigations of Pneumocystis, but also of other similar human-to-human transmitting pathogens." And also, they noted a very long interval between transplantation and development of Pneumocystis. The median was around 18 months. Azar attested that "based on the increasing incidence of sporadic Pneumocystis so far after transplant, there's a new movement now pushing for lifelong prophylaxis."

The team, led by Azar and Maricar Malinis, MD, FACP, FIDSA, FAST, the senior author, published their findings in "Genetic and Epidemiologic Analyses of an Outbreak of Pneumocystis jirovecii Pneumonia among Kidney Transplant Recipients in the United States," published in *Clinical Infectious Diseases*.

The biggest takeaway for Azar was the collaboration involved with understanding and mitigating the outbreak. When describing the workflow, he remembers, "So it was initially led by Infectious Disease, with Nephrology very closely involved. We had meetings together. Pharmacy was key in helping us pull the records of infusions, of doses, of timing, when the patients were in clinic, and when they weren't. The second author, Elizabeth Cohen, Pharm D, and I worked extensively on the analysis. We had to pull in statisticians from the Yale School of Public Health. We collaborated with NIH. This whole thing took more than a year of work."

And absolutely, for a physician who has come back to Yale four times—from a medical student from Lebanon to a post-doctoral research fellowship to an infectious disease fellowship and now, as an assistant professor of medicine, this effort amongst Yale departments and physicians is a prime example of why he keeps returning. "There's this really wonderful mix of people that are friendly, but really amazing scientists and clinicians at the same time. Yale has a very friendly atmosphere. We're all working together," Azar chuckled. "Ever since I came to the United States, this was the first place I called home. And it's

almost like a duckling being imprinted I think, it imprinted on me."

More information: Marwan M Azar et al, Genetic and Epidemiologic Analyses of an Outbreak of *Pneumocystis jirovecii* Pneumonia among Kidney Transplant Recipients in the United States, *Clinical Infectious Diseases* (2021). [DOI: 10.1093/cid/ciab474](https://doi.org/10.1093/cid/ciab474)

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