# New Horizons in Infectious Disease Treatment and Prevention in Immunocompromised Patients

The 5th Symposium on Infectious Disease in the Immunocompromised Host emphasized new opportunities and the next generation of researchers.

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As immune function wanes, people become vulnerable. What should be a sniffle becomes deadly pneumonia. Infections that should remain dormant awaken to fatal effect. An obscure fungus kills.

People with weakened immunity need tailored, expert care from infectious disease specialists. Every two years, Fred Hutch Cancer Center convenes the Symposium on Infectious Disease in the Immunocompromised Host to help ensure that these specialists stay at the forefront of their field. The fifth such symposium convened in Seattle in May.

Experts and rising stars in the field met to share practice-changing research, discuss tricky cases and outline new challenges and opportunities cresting the horizon. The nearly 350 attendees hailed from 140 institutions across 19 countries.

Just a generation or two old, the field must focus on ensuring a robust cadre of new infectious disease doctors specialize in immunosuppressed patients, said Michael Boeckh, MD, PhD, who heads Fred Hutch Cancer Center's Infectious Disease Sciences Program, which puts on the symposium.

Boeckh noted that the first two generations of specialists cleared major hurdles that made bone marrow and solid organ transplant possible. Now, the field must connect clinical and laboratory efforts to tackle the growing number of immunocompromised patients, new infectious threats and the accelerating difficulty of antimicrobial resistance.

"We have a vibrant, expansive, challenging, ever-changing area of practice. Our field is very dynamic, and there are unlimited opportunities for research investigation and for clinical practice," said Duke University infectious disease expert Barbara Alexander, MD, who co-chaired with Boeckh a panel discussion on training the next generation of infectious disease doctors specializing in patients with suppressed immunity.

Fred Hutch's president and director, Thomas Lynch Jr., MD, opened the symposium.

"What a tremendous opportunity for us to get together and talk about our science, talk about what's happening in our field in a collegial, supportive, remarkable, wonderful society," Lynch said. As a lung cancer oncologist who has collaborated with infectious disease specialists throughout his career, Lynch spoke of his own experience with outstanding infectious disease doctors and how their insights shaped his approach to cancer care. He holds the Raisbeck Endowed Chair.

"That tradition of excellence pervades everything you folks do," he said. "I've been incredibly impressed with the commitment and the focus and how much of a difference it makes."

Attendees also heard about progress toward a clinical trials network dedicated to the needs of people with weakened immune systems.

These people are often left out of trials of new vaccines and drugs, but Fred Hutch's infectious disease clinician-scientist Josh Hill, MD, FIDSA, is leading the effort to build the ImmunOptimize clinical trials network, a proposed public-private partnership dedicated to testing preventive and therapeutic interventions for infections in people with diminished immunity.

## Immunocompromised: more vulnerable, less studied

As of 2021, the National Health Interview Survey calculated that 7% of the U.S. population (more than 23 million people), were immunosuppressed. Reflecting their higher susceptibility, about 30% of people hospitalized for infections have compromised immunity.

Most people in the U.S. become immunosuppressed due to cancer treatment, bone marrow transplant or solid organ transplant. According to the U.S. Cancer Statistics, in 2021, nearly 1.8 million people were diagnosed with cancer. In 2022, more than 22,500 Americans received bone marrow transplants and in 2024 over 48,000 solid organ transplants were performed in the U.S. People may also receive immunosuppressive treatments to curb diseases like Crohn's or rheumatoid arthritis.

But despite their growing numbers, people with weakened immune systems are often left out of trials testing vaccines and drugs. The COVID-19 pandemic highlighted just how vulnerable immunocompromised people are, not merely to well-established infections like influenza, but also emerging infections, Boeckh said.

"Once again, immunosuppressed were basically left behind not only in the studying of vaccines but also drugs for a long time," he said. Hobbled by lack of information on vaccine efficacy, Boeckh and other infectious disease experts crafted recommendations for their immunosuppressed patients without data to draw on.

Still, the few studies done in this group highlight how much scientific research can shape care. A higher dose or second dose of the flu vaccine can help improve immunity in immunosuppressed

people. But this doesn't work for every vaccine or for every patient.

Infectious disease specialist Camille Kotton, MD, clinical director of Massachusetts General Hospital's Transplant Infectious Disease and Immunocompromised Host Program, discussed novel vaccines and monoclonal antibodies for respiratory viruses, including respiratory syncytial virus, or RSV.

This virus causes a lot of disease in immunocompromised people, but those younger than 60 are not currently included in the Center for Disease Control and Prevention's RSV vaccination guidelines. This means that for people who fall outside the recommended age ranges, insurance won't cover vaccination —which can cost several hundred dollars in the U.S. Asking people to pay out of pocket for a vaccine can enhance financial inequities, Kotton noted.

If doctors extrapolate from the flu and COVID-19 vaccines, they might recommend a second dose to immunosuppressed patients.

"That seems just transplant 101, right?" Kotton said. But she pointed out that in two recent studies on RSV vaccination in immunocompromised patients, a booster dose didn't improve immunity: "Not what we usually expect."

Getting a second dose, just to be safe, might be a costly and unnecessary decision, she said. Different patient groups may also respond better to different timing, Kotton noted. Solid organ transplants should get vaccinated for RSV prior to transplant, but it's still unclear when BMT patients would best respond to the vaccine.

Data supports CDC recommendations and insurance coverage, and can help non-infectious disease experts make clinical decisions. Alexander noted that 208 million Americans live in areas without access to infectious disease physicians, let alone those specializing in immunocompromised patients.

However, recent changes in the national vaccine approval systems may further hamper proposals to get immunosuppressed patients access.

ImmunOptimize, the proposed clinical trials network, would dramatically expand horizons for immunocompromised patients. Such an infrastructure, modeled after trial networks for cancer and bone marrow transplant, would make it faster, cheaper and easier to run clinical trials on vaccines new and old, as well as on new therapeutics, in the people who need them most.

Last September, stakeholders across disciplines met at the inaugural ImmunOptimize workshop in Washington, DC, to brainstorm strategy and present the idea to congresspeople.

At the ID Symposium, Hill presented the progress toward their goal. With Boeckh and Fred Hutch infection prevention expert Steven Pergam, MD, MPH, Hill has formed an advisory committee of infectious disease leaders from across North America, including Vanderbilt University Medical Center pediatric infectious disease expert Natasha Halasa, MD, MPH, who are committed to

creating an infrastructure that will fast-track the trials their patients need.

Halasa, who also joined the Capitol Hill tour in September, has administered flu vaccine trials and knows firsthand how the infrastructure and funding of a dedicated trials network could accelerate data.

The team is working to draw in experts in various areas, including pediatrics, cellular immunotherapy, solid organ transplant and trial implementation. They're exploring various funding avenues, including working with legislators and private donors to secure support for a pilot trial.

At the May symposium, they also convened a meeting with stakeholders across academia, industry, and patient advocate organizations to explore partnership opportunities.

Lymphoma survivor and Fred Hutch patient advocate Kaley Karaffa, who joined the stakeholder meeting and Hill tour, shared her experience fighting a mysterious infection that threatened her life and clinical trial eligibility. She also described how dangerous a lack of understanding or appreciation for immunocompromised patients' vulnerability can be, after watching a friend's parent undergo repeat hospitalizations for preventable infections during their cancer treatment.

A trials network must include advocates and help educate patients, she said.

"How can we have this [infection prevention] be a concept that resonates with cancer patients at the beginning stages of their treatment and diagnosis?" Karaffa said. "During their planning for, 'How can I be healthier throughout this and healthier afterwards, and ensure my treatment can be successful?' We can message the importance of keeping people healthy, especially those among us that are the most at risk."

## Changing landscape, new opportunities

A lot has changed since the late Joel Meyers, MD, demonstrated the power of preventing cytomegalovirus, or CMV pneumonia to save BMT patients' lives.

Meyers was among the first to study infectious diseases that affected transplant recipients and founded the Infectious Disease Sciences Program at Fred Hutch. As new immunosuppressive drugs and new treatments for cancer and autoimmune disorders reach patients, the field remains in flux, Boeckh said.

"The whole spectrum, how to serve the immunocompromised host has really gotten bigger," he said. "In the early days, we were all focused on mortality, critical illness, hospitalization. Those are still super important. But now recently, realizing as things all get better, that there's many other aspects, long-term disability, short-term disabilities, symptomatic disease, and the outpatient setting [that we need to focus on]."

New technologies to precisely diagnose infections are revealing how often they lurk behind generic

symptoms like the fevers that dog immunocompromised patients. In as many as half the cases of meningoencephalitis, pneumonia, sepsis and acute severe hepatitis in people with immunosuppression, the cause goes undiagnosed, said Charles Chiu, MD, PhD, a professor of laboratory medicine at the University of California, San Francisco.

Despite multiple diagnostic tests, diagnoses often prove elusive. Chiu presented findings showing how the precision and sensitivity of diagnostic tests can be improved by combining cutting-edge DNA sequencing methods that detect a wide range of pathogens with patient responses.

Presenters also discussed how different vaccine modalities and monoclonal antibodies are changing the landscape of care for viral infections. Strategies like cellular immunotherapy are moving beyond the cancer arena and being tested against infections like adenovirus.

While some viral infections that menace immunocompromised patients (like RSV and flu) have vaccines, others (like CMV) don't. University of California, San Francisco infectious disease expert and CMV researcher Ajit Limaye, MD, discussed promising results from a CMV vaccine.

"Do we even need new strategies for CMV prevention in the era of antiviral prophylaxis and diagnostic testing that we have?" Limaye asked. "I think the answer is yes. … I will hopefully convince you that the hope is likely higher than the hype."

Fred Hutch pulmonologist Guang-Shing Cheng, MD, presented work highlighting how respiratory infections, particularly RSV, can exacerbate or even trigger lung-related complications of cancer treatment. More work is needed to understand how this occurs, and Cheng is studying how repeated exposures to RSV may contribute to bronchiolitis obliterans syndrome, which can affect lung transplant and bone marrow transplant recipients.

Antimicrobial resistance is an ever-looming threat. It may take only a handful of years after a newly described (and apparently harmless) microbial species spreads across the world and picks up drug resistance. And immunocompromised patients are most likely to become infected with these strange microbes.

But there's hope. New strategies to tackle bacteria and fungi are on the horizon. The University of Melbourne's Monica Slavin, MBBS, FRACP, presented new antifungals under development that work through different mechanisms than current drugs.

"There's much potential for combination therapy," she said. "One of the huge implications of these new antifungals is that now we have drugs with very distinct spectra of activity. We are going to need to up our ante with diagnostics. We need to know what we're treating."

## Next generation: mentors make the difference

Attracting enthusiastic young clinicians and researchers will be critical to sustaining and growing the field, attendees said. The symposium is designed to help foster this, Boeckh said.

“This symposium began to honor Joel Meyers, now it’s focused on the next generation,” he said.

Trainees who attend the symposium are matched with mentors and have their travel, lodging and other expenses covered by educational grants provided by ID Symposium partners like Takeda Biosciences.

This year’s symposium included a panel of experts who discussed ways to improve training infrastructure, particularly in pediatric infectious diseases, and draw new providers, including advanced practice providers like nurse practitioners and physician assistants, into the field. Panelists also discussed how to keep the field nimble as the landscape of immunosuppression continues to evolve.

Unlike specialties with impressive paychecks, it’s usually the love of the work and a charismatic and supportive mentor that inspire trainees to commit themselves to this specialty, participants said.

Just as Boeckh was mentored by Meyers, he has mentored many of the up-and-coming leaders in the field.

Ria Mohan, an undergraduate student at Virginia Commonwealth University, presented one of the symposium’s top abstracts, studying risk factors for HSV reactivation in BMT patients. She’d performed the work as an IDS Summer Intern under the mentorship of Pergam and University of Washington and Pergam Lab epidemiology graduate student Molly Fischer.

“Steve [Pergam] is really great about making students and trainees feel empowered and uplifted,” Mohan said. “He’s uplifting trainees in a way they feel like they are the face of something huge and they feel they’re doing really big things and making significant progress.”

Mentors who also help mentees gain mentorship experience are doubly powerful, Fischer said.

“It’s crucial just having that supportive environment, especially for early-career researchers,” she said. “Having someone who is an expert in the field, but who is also just a very kind person, is really wonderful. He [Pergam] has trained me how to become a mentor as well, which I think is a really special opportunity to have.”

She and Mohan will be able to count on Pergam as long as they need.

“When you mentor someone, it’s long-term, not short-term,” Pergam said. “The goal is to be a support system as long as they need it. I had great mentors — Dr. Boeckh as an example — but also including people who are not in my own institution. They’ve given me opportunities that allowed me to move forward and grow as a researcher.  We need to commit to mentoring the next generation, because you can see how this conference demonstrates not only the amazing science but also how supportive our community really is.”

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