Advances in infectious disease treatment promise to expand the pool of donor organs

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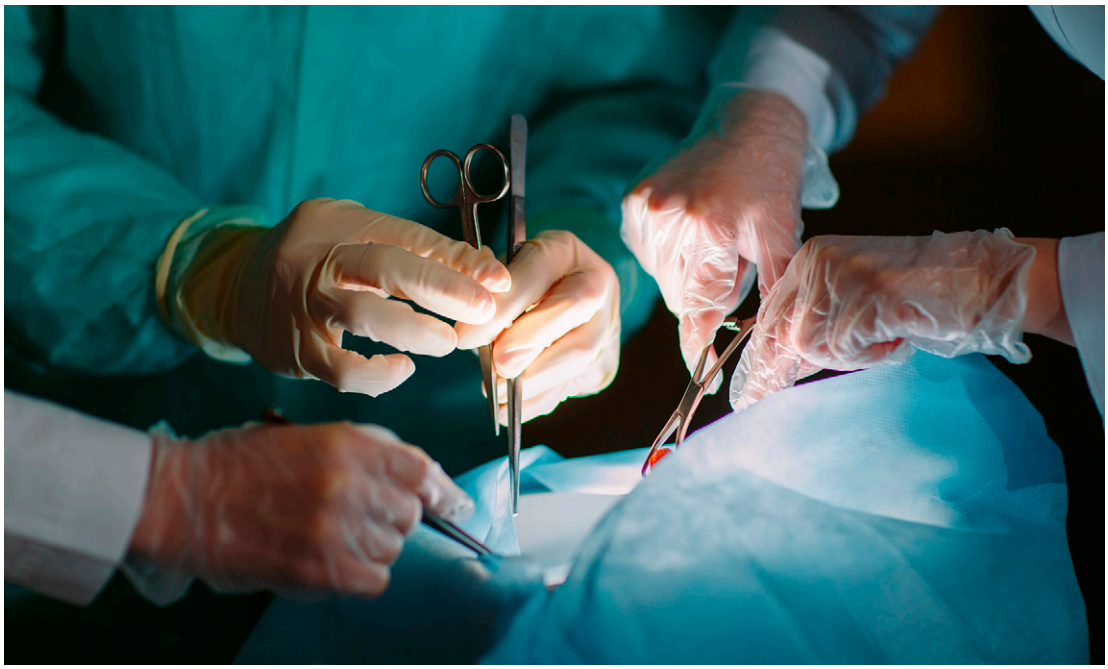
More than 109,000 people in the United States were awaiting organ transplants in November 2020, and approximately 17 die each day before receiving one (1). Seeking to expand the pool of organs available to these patients, clinicians are beginning to look to sources once considered off-limits: organs from deceased donors with infections such as HIV and hepatitis C.

At first, the notion of knowingly giving an organ from an infected donor to an immunosuppressed transplant recipient seems unthinkable. But a better understanding of the diseases caused by certain pathogens, as well as the availability of new drugs to treat or even prevent infections, mean that donor organs once discarded can now be used successfully. In recent years, this principle has been demonstrated dramatically via a series of hepatitis clinical trials: Organ recipients treated prophylactically with new, highly effective hepatitis C (HCV) medications were protected from infection after receiving organs from HCV-infected donors.

This proof of concept was made possible in 2013, with advances in a curative new class of HCV drugs known as direct-acting antivirals. And it comes at a time when the opioid epidemic has, for tragic reasons, increased the potential supply of deceased organ donors—many of them infected with HCV. But researchers are also exploring ways to safely use organs from donors infected with other viruses, including HIV, as well as other pathogens. In all cases, making more organs viable requires not only an effective treatment and reliable tests to detect infections but also building the confidence of patients and doctors.

Organ recipients and their physicians have always had to carefully weigh the benefits and risks of transplantation—including lifelong immune suppression and some "acceptable" possibility of infections.



Making more organs viable for transplant requires not only an effective treatment and reliable tests to detect infections, but also building the confidence of patients and doctors. Image credit: Shutterstock/David Tadevosian.

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"Maybe I'm okay with a person potentially acquiring hepatitis B if it gets them a life-saving transplant, and they can take a pill to keep it dormant," says infectious diseases physician Cameron Wolfe at Duke University in Durham, NC. "We now feel relatively comfortable with organ donors who may have passed away with hepatitis C or some bacterial infections, whereas in the past, clinicians might have shied away from that."

New research is aimed at further expanding that comfort zone. Although challenges remain, such as the high cost of HCV drugs, the difficulty of conducting transplantation trials, and social stigma around some diseases, clinicians see room for progress. In 2016, for example, researchers at Johns Hopkins University School of Medicine in Baltimore, MD, transplanted kidneys from deceased HIV-positive donors to HIV-positive recipients; the researchers performed the procedure with a living donor for the first time in the United States last year. "In an environment of shortage and scarcity, we're always trying to innovate and weigh the risks and benefits for those who don't have another option at that moment," says associate professor of medicine and oncology Christine Durand of Johns Hopkins, who co-led that study.

Continuum of Risk

In all transplantation, clinicians must flood the recipient's body with immunosuppressants to minimize the chances that the body will reject a grafted organ. As a result, transplants have always been carried out under threat of infection. "There's an infectious component to every transplant," says infectious disease physician Ann Woolley of Brigham and Women's Hospital in Boston, MA. "It's just about which infections we are able to manage."

Based on guidelines from the Organ Procurement and Transplantation Network (OPTN), potential living and deceased donors are screened for many common infections including HIV, various herpes viruses, syphilis, toxoplasma, and more. Clinicians then make decisions on the risks and benefits of transplanting each organ in the context of the donor and recipients' health. For instance, a donor who died of influenza, which mainly affects the lungs, may be able to donate kidneys or other organs. Similarly, donors with bacterial meningitis or bloodstream infections that were treated before death may be able to contribute organs.

Some of the most common infections that transplants are known to transmit include cytomegalovirus or Epstein-Barr virus, which each infect approximately 50% to 80% of adults in the United States (2, 3). In most cases, doctors try to match donor and recipient for cytomegalovirus status. With Epstein-Barr virus, however, if an organ recipient hasn't been exposed to the virus but a donor has, the transplant can increase the recipient's chances of developing some kinds of cancers. Still, these infections don't rule out using an organ; each infection can be controlled with medications that would be added to the treatments a patient might receive before or, Woolley says.

"In cases where you know there's an infection, you can make a calculated decision," Durand says. "We're more cautious when we don't know the cause of death, especially if it could have been an infection."

Guidelines for screening protocols that aim to reduce the risk of such infections are based on past lessons learned. For example, a 2009 case report in New York described a kidney transplant in which a living donor transmitted HIV to the recipient; the physicians concluded that living donors should be tested for HIV much closer to the date of transplant surgery and need to be advised to avoid exposing themselves to a new infection before transplant (4).

Even so, the authors of the report noted that the 2009 case represented the first confirmed transmission of HIV via organ transplantation since 1989 and the first in the United States since laboratory screening for HIV became available in 1985. And at the time of that incident, Durand says, tests for HIV and HCV in prospective donors weren't "quite as good" as modern-day tests because they depended on detecting antibodies, which take some time to appear after an infection. "So, we were missing a proportion of new cases. With newer tests, [missing these cases is] much less likely."

Better detection of infected organs is one step toward ensuring safe transplants. But safely transplanting organs from donors infected with certain pathogens is a new frontier. Getting there requires new treatments, better understanding of disease, and building the confidence of potential organ recipients, despite setbacks.

As early as 1991, clinicians at the New England organ bank (comprising several hospitals in the region) attempted transplants of HCV-infected organs to uninfected recipients. Because hepatitis C is a slow-moving infection that typically takes decades to cause cancer and liver failure, researchers thought such transplants might be feasible. But they found disease transmission rates as high as 82%, higher rates of damage to transplanted organs, and blood vessel abnormalities after heart transplants (5, 6). "Initially, the sense was that it was okay [because] it's such a slow-progressing disease," Durand says. "But after these outcomes were reported, the idea was shelved."

Building Evidence

Since the development of direct-acting antivirals for hepatitis C that block viral reproduction and eliminate the pathogen, small trials have established how the drugs can be used by organ recipients, whether before or immediately after transplants, to minimize the risk of infection. But given the highly individualized nature of transplants, randomized trials are difficult to conduct. And transplants from HCV-positive donors are already occurring outside organized trials. "So, it's mostly collective evidence from the community," says infectious diseases

physician Ajit Limaye of the University of Washington in Seattle.

In 2017, researchers at the University of Pennsylvania in Philadelphia conducted one of the first trials, transplanting kidneys from HCV-positive donors into 10 uninfected recipients. The virus reached detectable levels in all recipients by the third day after transplant. But, after a course of treatment with the new drugs, all were cured of their infection within 12 weeks, with relatively few side effects (7).

In 2019, Woolley and her colleagues at Brigham and Women's Hospital completed one of the largest such trials. They transplanted hearts and livers from HCV-infected donors in 38 HCV-negative patients. A four-week course of medication immediately after the procedure successfully prevented transmission of the virus. There were more cases of acute cellular rejection of grafted organs in recipients of HCV-infected lungs relative to a group that received uninfected lungs, but after adjusting for confounders such as donor ischemic time and underlying pulmonary disease in recipients the difference didn't reach statistical significance (8).

Despite the difficulty of doing large-scale randomized studies, researchers hope to keep accumulating evidence for the feasibility of using organs from HCV-infected donors. As with other diseases, they see two strategies for use of the organs in uninfected recipients: either prevent infection in the recipient with prophylactic doses of antiviral drugs, or wait until the virus reaches detectable levels in transplant recipients and then treat the infection. "Preventing the onset of infection is better than having to manage it," Woolley says. "But unfortunately, there are still limitations to access to these medications due to insurance issues."

The game-changing HCV drugs have been controversial among insurers from the start, because of their high price tag of around $80,000 for a 12-week course (9). And because hepatitis C previously disqualified organs, so it was not commonly expected in transplants, these costly drugs are not bundled into insurance-covered transplant medications such as immunosuppressant drugs or other preventive antimicrobials. "The problem is that in the real world you have to wait for insurance to give you the drugs and that can cause delays, and potentially complications, because of the hepatitis C," Durand explains.

Room for Improvement

Although improving access to drugs would help, the greatest barriers to using organs from donors with infections may ultimately be societal. Continuing stigma associated with homosexuality, drug use, or other behaviors linked to HIV, hepatitis C, and other infections tends to leave both physicians and patients reluctant to accept certain organs.

Hundreds of organs labeled as "increased risk" because of the presence of certain pathogens go unused each year, according to a 2017 analysis (10). This is in part because patients are less likely to accept the organs, some studies suggest (11). Adding to existing biases, clinicians also need to improve how they explain the risk of infection or inferior outcomes to ease organ recipients' concerns, Durand says.

"In cases where you know there's an infection, you can make a calculated decision. We're more cautious when we don't know the cause of death, especially if it could have been an infection."

–Christine Durand

But the ability to donate organs can be exceptionally meaningful to donors who were traditionally labeled "high-risk" and have often felt ostracized or socially inferior. People who are positive for HIV, for instance, are unable to donate blood (12). "It's hugely refreshing to my HIV-positive patients that they can now become organ donors, in a way that's hard to quantify," says infectious diseases physician Cameron Wolfe of Duke University. "I had one woman burst into tears—for her, it provided great meaning to be able to donate an organ. There's still so much stigma, and this kind of took that away for her."

Currently, organs from HIV-positive patients are only transplanted into HIV-positive recipients. But there may be room for further expanding the recipient pool, researchers say. In 2018, doctors performed a liver transplant from a living, HIV-positive donor to her uninfected 13-month-old daughter. The child, who had been experiencing end-stage liver disease, received prophylactic antivirals before the procedure, although physicians continue to monitor her HIV status in case she tests positive. The procedure was the first of its kind (13). But because HIV is now a highly manageable infection (most patients live healthy, symptom-free lives on a single daily pill), Durand says it's possible that this kind of transplant could one day become more feasible (14).

In principle, any advances in treating diseases that are poorly understood today can make more organs salvageable for transplant in the coming years. In 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has once again reduced the number of available organs because of the high risk of disease transmission—both to recipients and to the surgeons involved—from potential organ donors who died of coronavirus disease 2019 (COVID-19). The effects of the virus on different individuals and different organs of the body are still too poorly characterized, and the available therapies remain largely unproven (15).

At present, "we would not think of doing [these transplants] because we could harm the recipient and even the healthcare workers," explains infectious diseases specialist Camille Kotton of Massachusetts General Hospital in Boston. But if we had better treatments and understood how the virus affects different organs, she says, "that may change."

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