Editorial Commentary

Expanding the pool: the use of hepatitis C RNA positive organs in lung transplantation

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Lung transplantation still remains the definitive treatment for patients with end-stage pulmonary disease. It provides health care providers the ability to not only prolong survival but improve quality of life for these patients. The success of this surgery is dependent on a number of variables such as the conduct of surgery. However, what is equally if not more important is the postoperative care that we tell patients will be continued for the rest of their lives. This care requires the use of immunosuppression to prevent immune graft injury as well as careful monitoring for opportunistic and chronic infections that may arise.

While major surgical and medical advancements have propelled long term survival following lung transplantation, one major flaw limiting its use is the overwhelming disproportion between the high demand for this life saving procedure and the low supply of transplantable organs. This schism between supply and demand is evident annually as approximately 1,000 patients die waiting for these organs and with thousands more continuing to wait (1,2). This mortality has been mitigated by institutional changes including the application of the lung allocation score (LAS) to treat those with high clinical acuity (3). However, ultimately, the permanent solution is to increase the donor pool. As a field, we have attempted to do so through technologic advancements such as *ex-vivo* lung perfusion which allow us to improve the quality of marginal lungs to make them transplantable.

Over the years, we have begun challenging what was previously defined as contraindications to transplantations. Lung transplantation has increased by 20% in the past 5 years mainly due to an increasing number of available donors who have died from drug overdose and this has really fueled the conversation of expanding the donor pool (4,5). Despite deemed increased risk due, these donors are an attractive option given they are typically younger and have fewer coexisting conditions that are associated with decreased recipient and organ survival. Currently, it is not common practice to offer HCV-positive organs to HCV-naive recipients due to ethical as well as clinical reasons. Because of this, many of these organs that were otherwise medically suitable for transplantation were not used due to the presence of the hepatitis C virus (HCV) infection in the donors (6,7).

In the past, solid organ transplantation with HCV-positive donors into HCV-naive recipients has led to significant chronic HCV infections in recipients, with HCV transmission to as many as 82% of the recipients (4,5). This becomes clinically relevant as some studies have shown increased mortality from liver disease and the development of accelerated graft damage to due graft vasculopathy among recipients from HCV-positive donors (6,7). Because of this, organs from donors that are at high risk of contracting HCV are deemed increased risk donations.

The use of these HCV-positive rejected organs may

help alleviate the need for lung transplantation and this was recognized decades prior to the opioid epidemic. In a survey of UNOS approved lung transplant programs in 1999, 72% of programs that responded to the survey considered HCV-positive donors for transplantation. While only 26 programs actually accepted seropositive lungs, only 8 programs reported a total of 14 HCV-naive recipients received HCV-positive lung allografts. Of the 14 recipients, 6 would go on to develop biochemical evidence of hepatitis. However, there were no reported HCV related deaths (8).

These results are not ubiquitous in the literature. Carreno *et al.* presented a small series of three patients who acquired de novo hepatitis C viral infections after lung transplantation. All three patients developed elevated liver enzyme levels after their transplantation and ultimately received a diagnosis of HCV. All three patients died within 1 year, two of which were attributed to hepatic failure despite adequate treatment (9). These results were later confirmed by Englum and colleagues who identified 28 HCV-naive lung transplant recipients who received lung allografts from HCV-positive donors in the UNOS database from 1994–2011. Compared to their low risk donor counterparts, HCV-naive recipients receiving lungs from HCV-positive donors experienced a shorter overall survival. They further analyzed that in the modern era, recipients who were HCV-naive at the time of surgery had a similar median survival to HCV-naive patients receiving HCV-negative lung allografts (10).

In recent years, the development of potent direct-acting anti-viral agents (DAA) against the HCV infection has revitalized this option to potentially become a feasible pool of donor lungs. In various cohort of patients who received kidney, liver, or heart transplants, early data has shown these new anti-viral agents provide the opportunity to treat this infection if acquired after transplantation (4,11-14). These results can be attributed to the increased availability of these new direct-active anti-viral agents against HCV with expanded efficacy against more HCV genotypes while improving safety profiles with limited drug interactions. Because of these new advancements and promising early results, the American Society of Transplantation convened in January 2017 to create consensus guidelines encouraging the exploration of this area (15).

In the same year as the American Society of Transplantation consensus guidelines, the Toronto group published one of the first case reports of a 44-year-old HCV-naive patient who was in extremis prior to accepting a deceased donor lung offer who tested positive for HCV by nucleic acid testing (NAT). The patient tested positive for HCV RNA at 2 weeks and received DAA treatment with undetectable HCV RNA at 1 year (16). This year, we have also reported a case of a 30-year-old patient with cystic fibrosis and chronic HCV infection. At the time of an accelerated pretransplant evaluation, the patient was found to have active viremia and received DAA treatment which resulted in undetectable HCV viral loads 5 days prior to surgery. She underwent bilateral lung transplantation from an HCV-viremic donor and was subsequently was re-infected. She underwent DAA treatment again and had SVR documented at 1 year with normal liver function (17).

These early limited results are confirmed by the much larger series reported by Woolley and colleagues. Over a 16-month period, Woolley and colleagues were able to successfully perform 36 lung and 8 heart transplants (18). In their reported experience of HCV-mismatched heart and lung transplantation, the investigators administered a shorter 4-week course of a pangenotypic antiviral regiment to prophylactically treat patients from HCV-infected donors. All 35 patients who accrued at least 6-month follow-up had excellent graft function and undetectable hepatitis C viral loads. While not statistically significant, when compared to HCV-positive lung transplant recipients, lung transplant recipients in this trial experienced less cases of acute cellular rejection requiring treatment (18).

Because of the nature of this trial, several differences in the reported groups are important to note. HCV-mismatched recipients associated with a lower LAS score and subsequently less critically ill. Moreover, both HCV-positive and HCV-negative donors were younger than the mean age of the overall donor pool in the US. While the shorter intensive care unit and overall hospital stay along may be more reflective of favorable recipient characteristics, organs from younger donors with less coexisting disease processes may also play a factor.

While these short-term results are promising, this study does not satiate the need for long term results. Currently, the long-term data on any solid organ transplantation following DAA treatment for de novo HCV infection is scarce but promising as well. Ultimately, only time will tell whether this endeavor will pay off for those who are in need of a lung transplantation. If these results prove to be successful, this may offer yet another tool for us to chip away at the overwhelming disproportion between the supply and demand for lung allografts.

Clinically, it is without a doubt that DAA treatment for HCV infection has and will continue to revolutionize our ability to offer lung transplantation to our patients with end-stage pulmonary disease. However, it is important to acknowledge that with this new expensive resource comes great social and financial burden. While in its early phase, the cost of

these expensive drugs is currently alleviated through academic and research-oriented funding. However, the transition to its use in the non-research setting will predictably be a difficult one. This will not only prove to be a financial burden for someone in our healthcare system, but the ubiquitous application of these financially taxing drugs may also introduce ethical concerns that we should ultimately be ready to address.

Despite the issues that may loom around the corner, the results from this single center study by Woolley and colleagues provides us readers with a strong insight into the potential of utilizing HCV-mismatch lung transplantation to alleviate continued need for transplantable lung allografts. This will ultimately improve our ability to provide access to organs that patients require in a more timely and safe fashion.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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