



# The new frontier of hepatitis C virus (HCV)-mismatched heart and lung transplantation

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Heart and lung transplantation remain the main treatments for patients with end-stage cardiac and respiratory failure.

Nevertheless, the major challenge in heart and lung transplantation continue to be the shortage of suitable donors that largely exceeds the available supply. As a result of such a disproportion, many potential recipients die each year whilst in the waiting list before transplantation or alternatively became too sick to undergo transplantation.

In the case of lung transplantation these data are exacerbated both by the particularly low rate (15–20%) of suitable lungs amongst an overall low number of multi-organ brain death donors (1,2) and by a wait-list mortality as high as 30–40% (3).

Considerable efforts have been made in this direction and significant advancements have been achieved with the ultimate goal of increasing organ donation and utilization utilizing new strategies.

First, the donors pool and the utilization of organs have been expanded to organs were previously considered not suitable (“marginal donors”) (4). Second, potential donors have been managed by trained healthcare experts instead of unqualified professionals with particular attention to increase the number of acquired consents from families (1). Third, clinical management of brain-dead donors in the intensive unit care have been optimized adopting clinical strategies previously shown to be effective in critically ill patients (5). Fourth, hearts and lungs from donation

after controlled (cDCD) or uncontrolled cardiac death (uDCD) (6) and the lobar living lung donor program (7) have been recently proposed. Fifth, *ex vivo* lung perfusion (normothermic *ex vivo* lung perfusion: EVLP) has been proposed to increase the number of available lungs through two major routes: first, the “reconditioning” of injured lungs toward clinical acceptability and second a more accurate and prolonged evaluation of marginal lungs prior to their implant; the use of an alternate list for cardiac transplantation (where two recipients lists are arranged and non-standard donor hearts, that would otherwise not been utilized, are matched with excluded potential recipients (8).

Among the more modern and innovative strategies it should be certainly included the successful use of organs obtained from donors with hepatitis C virus (HCV) infection in recipient candidates who do not have HCV infection (so-called HCV-mismatched transplantation) as recently published by Woolley and Coll (9), Galasso and Coll (10) and Rhondalyn and Coll (11).

The concept is not new since case reports have been previously published for kidney (12,13), lung (14,15) and heart transplants (16,17). In 2017 the Consensus Guidelines by the American Society of Transplantation have provided recommendations in an attempt to discipline this area and better empower further research (18).

HCV-mismatched transplantation is a fascinating clinical model for a number of reasons. First, the new generation

of HCV-treatment drugs provide a cure rate (defined as sustained virologic response at 12 weeks) that approach 100%. Available agents such as direct-acting antiviral agents (DAA) are active against multiple HCV genotypes, offer a safe pharmacological and pharmacokinetic profile and present a relatively limited amount of side effects (especially on kidney and liver function) and, more importantly, have no considerable drug interactions making clinicians far away from the pioneering era of the Interferon-based treatments when endothelial or vascular injury or severe liver toxicity were common, together with the risks of exacerbating allograft rejection due to the up-regulations of the immunologic response in the recipients (16).

Second the usual pool of HCV-positive donors—due to the unprecedented public health crisis related to opioid misuse/dependence worldwide (19)—usually consists of young drug-abusers, healthier than standard donors without HCV infections and predominantly with less co-morbidity. This may theoretically reflect into an improved organ pool of donations with expected superior outcomes in terms of both graft and donor survival.

According to the WHO, in 2017, a population of 71 million of people with chronic HCV infection are globally estimated (20), hence rendering the donor pool and the number of potential donations significantly enlarged.

Although preliminary, available data should be considered encouraging especially because they markedly address a broad pool of donors.

The paper published by Woolley *et al.* (9) has some unique features that must be considered. First, it is a somewhat large series of patients (44 in total, 8 heart and 36 lung transplantations); second, it is one of the first report of HCV-mismatched lung transplantations; third, the course of administration of the pan-genotypic antiviral regimen to treat recipients was started immediately after transplant via feeding nasogastric tube and it was relatively short in duration (4 weeks). With this approach the Authors achieved a surprisingly 100% viral response.

This report undoubtedly provides support for further consideration of organs from HCV-positive donors for heart and lung transplantation candidates. However, as pointed out by the authors themselves, these results should be regarded with caution and could not be generalized for a number of reasons.

First, the follow-up time is very short (6–12 months) and nothing could be anticipated on long term outcomes.

We know from previous series that some of the recipients from HCV donors have an increased incidence of

cardiovascular morbidity (16) as well as other non-specific metabolic complications. Moreover, the activation of the immune system related to *de novo* viral infection may lead to unintended consequences, including organ rejection, additional severe infections and lethal complications, especially if organ donation is extended to critically ill non selected candidates.

Second, it is not demonstrated if the short course of DAA therapy is successful in maintaining a sustained prolonged viral response or if patients are ultimately going to relapse with HCV infection; in case of relapse, if they can be treated again with a second course of therapy and for how long and eventually if any relapse could be avoided with a longer course regimen of cure. We also know that the risk of acute infection in the setting of immunosuppressant could occasionally lead to rapid viral replication and in order to possible benefit the patient the level of HCV RNA should be closely monitored to implement early treatment.

There are also some practical and ethical issues that could not be ignored. DDA therapy despite efficacious is expensive outside research trials; we have learnt that this treatment should be better administered in the early period after transplantation when the HCV viral load is small and should be accessible in advance when the suitable HCV donor is available. We should be also prepared to lung transplants recipients that will refuse HCV infected organs for several emotional and socio-ethical reasons: what happens to those who refuse? Do they remain on the waiting list as and do continue to wait for a suitably matched organ or do they drop off from the list?

All these are open questions that need to be answered in the near future as large-scale multi-centre trials assessing the utility of to accepting HCV-mismatched donors is are definitely needed.

These findings should be expanded also to people with HIV infection that can be cured thanks to the availability of triple-combination antiretroviral therapy (cARTs) (21). Most organs from HIV-positive deceased donors have been implanted into HIV-positive adult recipients, including the paediatric HIV-positive population. The large number of HIV-infected individuals on cART is an unutilised source of otherwise eligible living organ donors (21). More recent advances in this field suggest the possibility to include as potential as living organ donors HIV-infected individuals and the possibility of offering organs to HIV-uninfected individuals from HIV-infected donors who are well-controlled on combination cART. While the post-transplant administration of DDAs to treat *in vivo* HCV-

mismatched patient is fascinating, recent data propose an even more attractive alternative: the inactivation of the virus in the harvested lungs through the EVLP circuit (10). The chance to eradicate the infection *ex vivo* within the organ “just before” transplantation looks really smart because can virtually avoid both the costs and the toxicity or at least the drug interactions related to antiviral medication and might resolve also the psychological barrier of the recipients to accept an infected organ with the plan of cleaning it in the immediate post-transplantation recovery time.

The efficacy of EVLP in diminishing HCV levels in donor organs was already reported as a case report (14). However, since viral replication seems not to occur within the harvested graft itself, the Authors added to EVLP, a combination of light irradiation (ultraviolet C) and photodynamic therapy (PDT) (methylene blue activated with red light irradiation), for pre-donation sterilization of blood components in the blood bank (22). With this technique the HCV infection was completely eradicated during the short period of time of the normothermic EVLP perfusion. This innovative technique proved to be effective both in human lungs and in pre-clinical animal lung transplant model in pigs.

Recent data suggest that *ex vivo* treatment to prevent donor-recipient transmission are feasible and effective in reducing post-transplant bacterial (23) and HCV load (24). However, (I) the lack of data on HIV+ donors, (II) the lack of information on intermediate and long-term outcome, leaves cARTs treatments the only option for HIV-infected tissues.

In conclusion, as organ shortages persist, the option of utilising living or deceased donor organs from people with chronic HCV or HIV+ viral infections deserves attention is going to be potentially relevant since the figures are self-explaining: currently only 15% of lungs from available donors are used (3); HCV affects 2% of North Americans and underuse of these organs is particularly relevant because if HCV-positive donors could be safely added to the donor pool it is estimated that at least 1,000 new donors for lung transplantation would be available every year in North America alone (1). These data confirm the urgency of provide solid evidence to allow reconditioning from infection of harvested human lungs or the treatment of recipients become infected after a mismatch transplantation.

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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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