


Progress towards solving the donor organ shortage

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Kidney transplantation is the best therapy for kidney failure, but is limited by donor organ availability and the risks associated with immunosuppression. Studies in 2022 provided encouraging data about the outcomes of COVID-19 among transplant recipients, the effects of changes to organ allocation policy in the US and progress in xenotransplantation, raising hope that the organ shortage can be solved.

Kidney transplantation is the preferred treatment for kidney failure, with transplant recipients enjoying increases in longevity and quality of life. However, the Achilles' heel of transplantation remains the shortage of available organs. As the supply of these life-saving organs is limited, only a minority of patients can realize the benefits. The past few years have offered additional challenges as the COVID-19 pandemic wreaked havoc on global health care systems. However, key studies published in 2022 have provided reasons for optimism regarding the future of kidney transplantation (Fig. 1).

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COVID-19 has dominated the attention of the healthcare community for nearly 3 years, and no area of medicine or patient population has been unaffected. COVID-19 is of particular concern for immunocompromised patients, and early studies showed increased mortality in this group^{1,2}. The risk to transplant recipients was less clear, but was suspected to be similarly increased. In 2022, a meta-analysis of 31 observational studies from the pre-vaccine era reported that receipt of a solid organ transplant was not associated with increased mortality up to 30 days after infection with SARS-COV-2, after adjustment for comorbidities³. Notably, organ transplant recipients did have increased 30-day COVID-19 mortality when data from studies without adjustment were included in the analysis. A subgroup analysis of the adjusted outcome data showed that kidney transplant recipients were not at increased risk of death from COVID-19 compared with the general population. Transplant recipients require monitoring of immunosuppression and therefore have frequent interactions with the healthcare system, so they might have benefited from early detection of infection and escalation of COVID-19 care.

Importantly, the meta-analysis also showed that transplant recipients were at more risk of ICU admission and acute kidney injury (AKI) owing to COVID-19 than the general population. This increased risk of AKI is notable given that most of the transplant recipients in the pooled analysis were kidney recipients. The data did not enable the authors to assess whether the risk of rejection or organ loss was due to COVID-19 itself or to reduction of immunosuppression in response to SARS-COV-2 infection. As most of the studies included in the meta-analysis were from the first wave of the pandemic, it is unclear whether the findings would extend to the subsequent waves of the Delta and Omicron variants, which had differing effects across regions owing to the timing of surges and social determinants of health. The effects of the later variants would also be confounded by increasing vaccine availability, use of novel therapeutics such as tixagevimab–cilgavimab and increasing rates of natural immunity owing to previous SARS-COV-2 infection.

In 2021, at the height of the pandemic, major policy changes were enacted in the US with the goal of increasing organ transplantation and decreasing geographic variability in transplant rates. Rather than the previous local–regional–national allocation system based on donor service areas (DSAs) and United Network for Organ Sharing (UNOS) regions, kidneys from deceased donors are now allocated first within a geographical circle with a radius of 250 nautical miles, then shared nationally if not used within that circle. Moreover, the Center for Medicare and Medicaid Service (CMS) revised their outcome measures for Organ Procurement Organizations (OPOs) with the aim of incentivizing them to be more aggressive in pursuing organ donation and recovery. The overall result of these changes is something to celebrate – 2021 saw more kidneys transplanted in the US than in any previous year, and 2022 is on track to exceed this record⁴. However, much work is still to be done. Organ discard rates are increasing and the simultaneous nature of the policy changes, enacted during a pandemic, makes accurate assessment of their effects challenging.

Key advances

- Organ transplantation is not an independent risk factor for death from COVID-19 when data are adequately adjusted for other comorbidities³.
- The performance of US Organ Procurement Organizations is not driven by the organ acceptance and utilization rates of local transplant centres⁵; policy changes could increase organ recovery, allocation and utilization.
- Successful transplantation of genetically modified pig kidneys into recently deceased humans is encouraging for the potential future of clinical xenotransplantation^{7,8}.

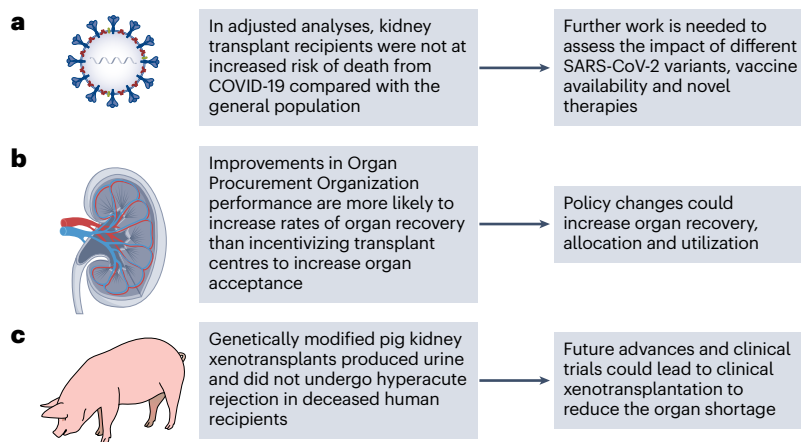


Fig. 1 | Major findings in kidney transplantation in 2022. Key studies reported in 2022 provided reasons for optimism regarding the impact of COVID-19 on kidney transplant recipients³ (a), the potential for US policy changes to increase rates of organ transplantation⁵ (b) and the future of kidney xenotransplantation^{7,8} (c).

Using data from before the 2021 change in donor kidney allocation, Doby et al.⁵ demonstrated that low-performing OPOs had low performance across all donor groups without consistent trends in kidney utilization or discard rates within the DSAs that they serve. This finding discredits a criticism of the CMS revision of outcome measures – that OPO performance is driven by local transplant centre organ acceptance practices. This criticism should be further abated by the 2021 changes in allocation policy, which effectively unlink OPOs from centres within their DSAs. Doby et al.⁵ clearly demonstrate that organ recovery, allocation and utilization are inextricably linked. As further policy changes are considered in the US, including a proposed move to a continuous distribution model free of any geographic boundaries, care must be taken to consider how such changes would affect each component of this triad.

The challenges of kidney allocation and utilization are driven by the shortage of available organs for transplantation. Decades of advocacy work to increase donation of kidneys from both deceased and living donors have been fruitful, but these successes do not outweigh the increasing prevalence of kidney failure. Indeed, annual additions to waiting lists exceed the number of kidney transplants performed each year and, until recently, the number of patients waiting for a transplant increased annually⁶. Ending the organ shortage and achieving durable immune tolerance have long been the ‘holy grails’ of transplantation. The past year saw a major step towards a possible solution. Two groups, working independently, reported the successful transplantation of a genetically modified pig kidney into a recently deceased person^{7,8}. In both studies, the transplanted kidney produced urine and did not undergo hyperacute rejection. This success builds on decades of preclinical research in nonhuman primates aimed at advancing xenotransplantation as a solution to the organ shortage, and represents a major step towards a future clinical trial. In preparation for such a trial, Porrett et al.⁷ also demonstrated the feasibility of performing pre-transplantation crossmatching across the species barrier. A negative pre-transplant crossmatch test is considered standard-of-care for kidney allotransplantation, so this proof-of-concept for xenotransplantation is another key milestone towards the clinic. The work of these two groups in 2022 was further bolstered by the announcement of a successful xenotransplant of a genetically modified pig heart into a human⁹. Together, these studies strongly suggest that clinical xenotransplantation is on the horizon.

“clinical xenotransplantation is on the horizon”

As we emerge from the COVID-19 pandemic, the goal remains to offer the benefits of kidney transplantation to as many patients as possible. Although the challenges of COVID-19 might finally be abating, kidney transplantation is still hindered by a lack of available organs. We must strive to make the most of the available donor organs via effective policies that address all phases of the transplant system (recovery, allocation and utilization) and to push forward with preclinical research in the hope that xenotransplantation or another advance will end the organ shortage.

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Competing interests

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