

Progress in Transplantation: Will It Be Achieved in Big Steps or by Marginal Gains?

Jeremy R. Chapman, AC, FRCP, FRACP

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A wish for progress in transplantation assumes that there are needs not met by the currently available therapy and that the barriers to resolving the problems can be surmounted. There are 5 major unmet needs: the potential to avoid transplantation either by prevention of disease or provision of an alternative to natural biological organ replacement; geographic heterogeneity of access to, and quality of, transplantation; availability of transplantation to those in need of it; survival of the patient and the transplant; and the avoidance of adverse effects of immunosuppression. During the past 50 years, there have been advances on at least 4 of these 5 fronts that illustrate the interplay of “big steps” and “marginal gains” in the following areas: surgical technique, testing the immunologic barriers, introduction of chemical and biological immunosuppression, and prophylaxis for microbial infections. The potential for further improvement comes in 5 major areas: blood biomarkers for monitoring of rejection, drug-free transplantation through the development of stable tolerance, eliminating the impact of ischemia-reperfusion injury, xenotransplantation of porcine kidneys, and finally, the possibility of autologous regeneration of functioning kidney tissue to treat advanced kidney disease.

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The concept of progress in transplantation evokes many different visions, dependent on the eye of the beholder. The health care payer may see progress as defined by reducing the cost and increasing the effectiveness of transplantation as an alternative to dialysis treatment for end-stage kidney failure. The clinician will see progress framed as both improved effectiveness and reduced waiting times

for transplantation. Patients and their families see progress measured by availability and quality of a new life after the threats and realities of end-stage kidney failure and dialysis treatment. In this Forum, I describe the most urgent or significant unmet needs, as well as the historical advances in which both “big steps” and “marginal gains” can be seen. Finally, I propose 5 areas in which we might expect progress through big steps or marginal gains.

The aligned need is to improve patient and transplant survival and minimize the adverse events attributed to the immunosuppressive drugs that tarnish the shining success of transplantation. Are these claims true? Do they constitute the “burning platform” needed to drive universal improvements? There is considerable variability between countries and it may be that a critical need in one environment is not present in another. Before accepting them as the critical goals for progress in transplantation, these claims must be critically examined.

UNMET NEEDS IN CLINICAL TRANSPLANTATION OF THE KIDNEY

You’ve got to be very careful if you don’t know where you are going, because you might not get there.

Yogi Berra¹

In news media in almost every country, there is an assumption that there is a greater need for transplantation than is being met by the prevailing rate of organ donation.

Prevention of the Need for Kidney Transplantation

The most effective therapy for chronic kidney disease (CKD) stage 5 is the preservation of glomerular filtration rate at earlier stages of CKD. The failure of modern society to improve nutrition and encourage physical activity leads to obesity, diabetes, and

From the Centre for Transplant and Renal Research, University of Sydney, Westmead Hospital, Westmead, NSW 2145, Australia.

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Address correspondence to Jeremy R. Chapman, AC, FRCP, FRACP, Centre for Transplant and Renal Research, University of Sydney, Westmead Hospital, Westmead, NSW 2145, Australia. E-mail: jeremy.chapman@sydney.edu.au

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hypertension, which initiate and advance CKD. Alarming, the increasing incidence of diabetes has yet to feed fully into the incidence of end-stage kidney failure in both developed Western societies and emerging economies.² Secondary prevention measures, implemented through primary care settings, can screen for disease and implement measures known to retard the progression of kidney disease, in particular blood pressure control, use of angiotensin blockade, and improving glycemic control. Effective preventive measures for other causes of CKD stage 5, such as the glomerulonephritides and inherited disorders such as polycystic kidney disease, are clearly important, but treatment options remain limited. The incidence of CKD stage 5 has recently stabilized in Australia, which provides some comfort that prevention strategies may deliver part of the solution.³

Global Availability of Transplantation

The World Health Organization publishes national statistics for transplantation annually as part of the Global Observatory on Donation and Transplantation.⁴ Kidney transplantation rates vary substantially by country, based on wealth and stage of development

reflected by the Human Development Index (Fig 1).⁵

It is one of medicine's greatest tragedies that human organ trafficking has been generated by the great disparities in access to transplantation and the ability of the rich to prey upon the poor and vulnerable. The health ministries of the world have responded to this problem through an agreement at the World Health Assembly in 1991, which was reaffirmed in 2010. The Declaration of Istanbul of 2008 enunciates the principles of ethical health policy and clinical practice.^{6,7} These 2 documents should be regarded as equally significant as the original Harvard ad hoc committee's report on brain death.⁸ They were undoubtedly big steps, but implementation has required a journey of a thousand small steps.

Number of Transplants in Relation to Patients Using Renal Replacement Therapy

The number of patients developing end-stage kidney failure globally is unknowable, but reliable estimates are available with advanced public health data. In developing economies, the incidence of end-stage kidney failure is hidden by undiagnosed disease, but it is possible to measure the incidence of dialysis treatment. This

approach demonstrates the disparities in treatment rates, which clearly show the relationship between national wealth and renal replacement therapy.⁹ The relationship between the proportion of patients treated by transplantation compared to dialysis is also closely related to national wealth (Fig 2), but there are other factors that influence this ratio. Norway, Costa Rica, and Namibia all treat >70% of their patients by transplantation, whereas Japan, Singapore, and Tunisia treat only 5% by transplantation. Even within the United States, it has been shown that the rates of transplantation vary greatly. For example, an analysis has shown that patients treated in dialysis units run by large for-profit chains have a lower likelihood of being placed on the deceased donor waiting list than those in small unaligned programs.¹⁰ Moreover, access to transplantation also varies considerably across the 58 donor service areas, with median waiting times ranging from 0.61 to 4.57 years.¹¹

In some countries (eg, Pakistan), transplantation is exclusively from living donors. The number of living donors might theoretically be sufficient to meet the needs of the community because of large family size; however, the impact of donation in such countries without

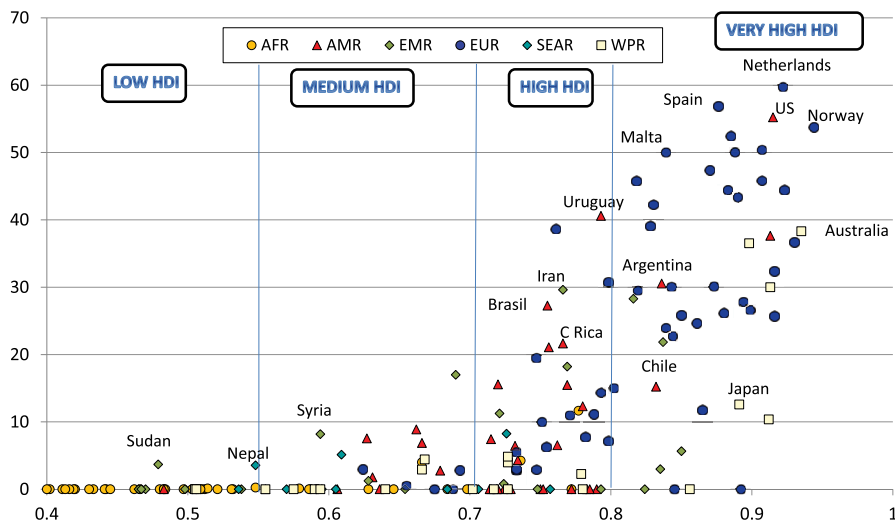


Figure 1. Kidney transplants per million population by Human Development Index, 2013. Reproduced from the Global Observatory on Organ Donation and Transplantation, a collaboration of the World Health Organization and the Organización Nacional de Trasplantes, with permission of the World Health Organization. Abbreviations: AFR, African; AMR, Americas; EMR, Eastern Mediterranean; EUR, European; HDI, Human Development Index; SEAR, South East Asian; WPR, Western Pacific.

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