Improved outcomes for paediatric renal transplant recipients

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Abstract

Pre-emptive living donor renal transplantation improves the morbidity and mortality of children with end stage kidney disease and is widely accepted as the gold standard for renal replacement therapy. As the accessibility to transplantation improves, its success is underpinned by the evolving importance of renal allograft matching and the principles of the immune mechanisms that lead the host response to engraftment. This coupled with the development of immunosuppressive protocols which have improved the renal allograft survival and simultaneous refinement of surgical expertise, allowing progressively younger children to undergo successful transplantation. Most importantly, advances have collectively improved the neurocognitive and psychosocial outcomes for children. However, despite great innovations, significant hurdles remain with improving outcomes for chronic allograft dysfunction and improving renal allograft survival. Unsurprisingly, best practice guidelines are debated with a growing shift from protocol based towards individualised therapy. In addition, immunosuppressive regimens are commonly associated with a significant increase in adverse effects, which correlates with a decline in adherence. Looking forwards, the global burden of transplantation outweighs the number of potential donors, therefore the legislative framework becomes more important to protect vulnerable individuals. This review explores transformative power of transplantation alongside the predicted challenges ahead.

Keywords paediatrics; renal transplantation; review

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Introduction

End stage kidney disease (ESKD) is Stage V chronic kidney disease, at which the glomerular filtration rate drops below 15 mls/min/1.73m^2 and whereby the kidneys are unable to match homeostatic metabolic demands. The global burden of children receiving renal replacement therapy is approximately nine per million age related population (ranging from four in Russia to 18 in New Zealand). The underlying aetiology of ESKD is heavily influenced by demographic differences, with congenital anomalies of the kidney and urinary tract predominating in the United Kingdom and United States of America whereas the Finnish cohort data reveal that congenital nephrotic syndrome is most prevalent cause. In both populations, haemolytic uraemic syndrome and glomerulonephritis featured, whereas focal and segmental glomerulosclerosis (FSGS) was not seen commonly among the Finnish cohort.

Dialysis has allowed clinicians to perform renal replacement effectively, although the literature highlights the significant neurodevelopmental and psychosocial impact to children undergoing dialysis and its accompanying restrictions. Additionally, these children are more likely to have poor longitudinal growth and studies have shown a subsequent improvement in quality of life following transplantation after adjustment for comorbidities, donor risk profiles and healthcare differences worldwide. Lastly the economic burden to healthcare systems is vast. Dialysis is estimated to cost approximately £31,000 per patient each year in the UK. For all these reasons, dialysis is viewed as a bridge towards transplantation for children, the gold standard method of renal replacement therapy.

Historical overview

The quest to replace failing organs has persisted for centuries and been represented countless times in history. Jaboulay performed the first human kidney transplant in 1906 using pig and goat donors, followed by Unger in 1909 with monkey donors. However, none of these early human xenografts functioned beyond a few days and their recipients perished. Subsequently, Carrel developed the technique of blood vessel suturing following engraftment and was recognized by the 1912 Nobel Prize. The first human donor to human recipient transplant took place in 1933 lead by Voronoy, however unknowingly the procedure was performed across a blood group mismatch, leading to acute allograft rejection and renal dysfunction. The limited success of these pioneers raised questions regarding transplantation, nevertheless, the lack of reasonable alternatives pushed pioneers in the field further. Long-term haemodialysis was unfeasible, as each attempt expended an accessible vessel, until Scribner devised arteriovenous conduits for longstanding vascular access in 1960.

Major advances in the immunology of transplantation is accredited to Medwar, whose 1950s experimentation of rabbit skin homografts were seminal in elucidating the timeframe and histological of rejection. Shortly afterwards in 1954, Murray's team performed the first successful isograft renal transplant from one identical twin to the other, however the archetypal problem of improving renal allograft survival through immunosuppression remained. Mustard derivatives and azathioprine were trialled with limited success alongside total body irradiation. The breakthrough came in 1963 when Starzl proposal a novel

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immunosuppression protocol with a >70% 1-year renal allograft survival, at a time which <10% would survive three months. Starzl recommended the co-administration of prednisolone alongside azathioprine, which could then be weaned gradually without provoking rejection. This proved the catalyst for transplantation as the Starzl "cocktail immunosuppression" remained the best practice for decades.

Allograft donation

Deceased donation

Traditionally transplant organs originated from deceased donors, so graft quality varied considerably depending on the degree of ischaemic insult. However, during the 1960s a controversial view was expressed that irreversible loss of brain function should be considered as a form of death despite ongoing cardiac contractility. Despite initial resistance from clinicians, this perspective has become widely accepted and has been instrumental in facilitating donation.

There has been an increase in the number of living donor renal transplants for paediatric recipients in the last decade in the UK (Figure 1) with an increase in altruistic donors, ABO and HLA incompatible renal transplants for children (Figure 2).

DCD occurs frequently following road traffic accidents, which has further increased after the Driver and Vehicle Licencing agency established donor status from everyone who obtains a driving licence. A fierce debate continues between clinicians and politicians alike, whether to accept the current stance of expressed consent or to move towards presumed consent, assuming the latter would increase donation as it shifts the position from active engagement to passive permission. Although opponents argue this weakens an individual's autonomy and removes the protection of vulnerable patients unable to consent. Wales was the first country in the UK, amid strict regulation towards presumed consent in July 2016. Despite increasing public awareness, at present there has not been a statistically significant increase in the rate of deceased donation. However, more time is required to detect a difference. Nevertheless, numerous countries with presumed consent have a lower donation rate than others with expressed consent, highlighting that cultural factors and awareness may be just as important.

Living donation

Numerous advantages are present with living donation, primarily it permits earlier pre-emptive transplantation with optimal logistical considerations, leading to increased renal allograft survival with greater haplotype matching and negligible ischaemic insults. Nonetheless, there are barriers, including the impact to the donor that stems from the consequences of invasive surgery. Lately, the introduction of minimally invasive surgery, such as laparoscopic live donor nephrectomy, has been associated with temporal increase in the living donation rate. Another hurdle is that related donors may be blood group or immunologically incompatible. To overcome this, the National Living Donor Kidney Sharing Scheme (NLDKSS) in the UK has been established. These programmes allow healthy incompatible donor and recipient pairs to enter the scheme to find more suitable matches through other incompatible donor/recipient pairs, non-directed or altruistic donor chain programmes.

Immunosuppression

Advances in transplantation have coincided with the introduction of powerful immunosuppressive agents. Due to the paucity

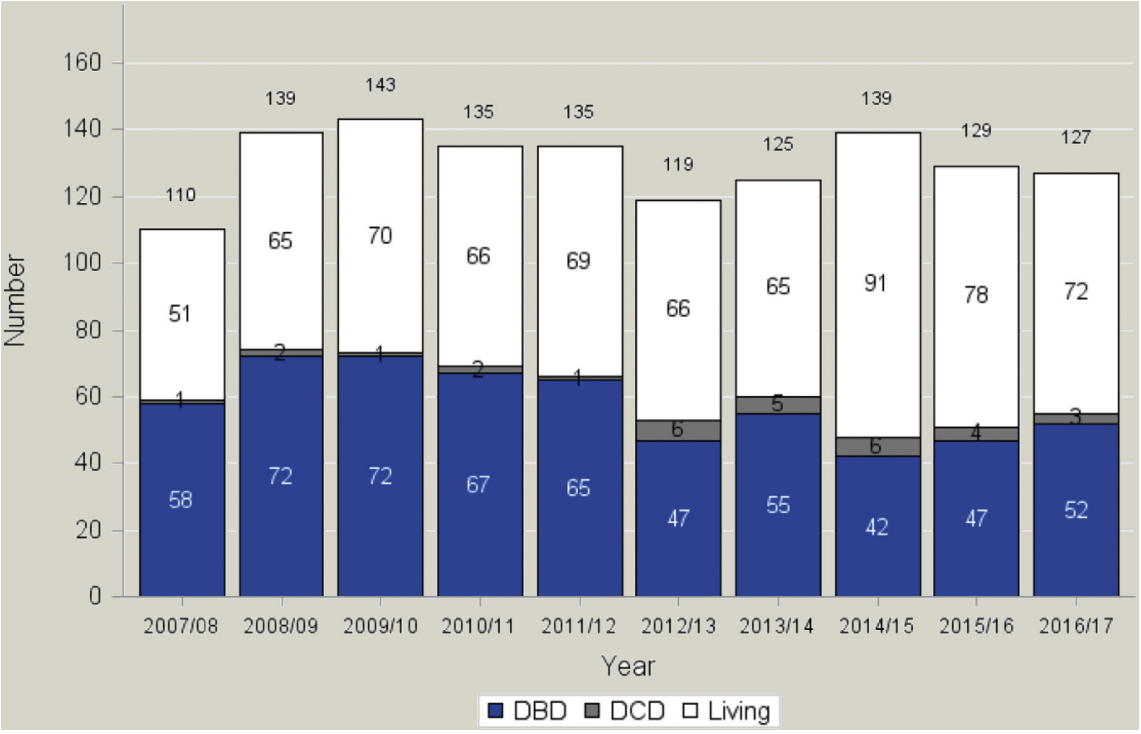

Figure 1 Number of living and deceased donor (DBD and DCD) paediatric kidney only transplants in UK (1 April 2007 to 31 March 2017).

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