Institution:
University of Cambridge

Unit of Assessment:
UoA1

Title of case study:
Increasing Access to Kidney Transplantation

1. Summary of the impact (indicative maximum 100 words)

Research led by Bradley, Watson and Pettigrew (Department of Surgery, University of Cambridge) since 2000 has improved patient access to renal transplantation significantly, changed UK kidney transplant policy radically, and informed policy internationally. Their findings have increased considerably the use of kidneys (and other organs) from circulatory death donors (DCD), including those with extended time to cardio-respiratory arrest, and primary brain malignancy. Their randomised trial of machine perfusion for DCD kidneys has informed NICE guidance, while their analysis of factors that determine transplant outcome in recipients of DCD kidneys has informed national guidance for DCD kidney retrieval and organ allocation policy at NHS Blood and Transplant.

2. Underpinning research (indicative maximum 500 words)

There is a worldwide shortage of organs for transplantation and increasing the number of deceased donor organs transplanted has been a major strategic initiative, addressed by research led by Cambridge academics in the Department of Surgery (Andrew Bradley, Prof of Surgery 01/08/1997 to present, Chris Watson, Senior Lecturer 01/10/2001-30/09/2007, Reader 01/10/2007 - 30/09/2011, Professor of transplantation 01/10/2011 to present and Gavin Pettigrew, Clinical Senior Research Associate 01/10/2003 - 30/09/2006, University Lecturer 01/10/06-30/09/2013, Reader 01/10/2013 to present). This research was published between 2008- 2012.

Patients dying from primary intracranial malignancy are a potentially important source of organs for transplantation but a perceived risk of tumour transfer to the recipient had previously limited their use. In 2008 Watson and Bradley (1) led research using information from UK Transplant and cancer registries and found no instance of tumour transmission from the 179 donors with a primary intracranial malignancy who gave organs to 448 recipients. The research team therefore concluded that organs from all patients dying from primary intracranial malignancy should be considered for transplantation, balancing the small risk of tumour transmission against likely mortality on the transplant waiting list.

Donation after circulatory death (DCD) donors are an increasingly important source of kidney transplants but the time to cardiac death following withdrawal of life-supporting treatment varies widely and is an important determinant of whether organ donation occurs. Because of concerns about ischemic injury during the agonal phase, many clinicians abandon donation if cardiorespiratory arrest has not occurred within one hour of controlled withdrawal of life-supporting treatment. Watson and Bradley (2) led a multicentre study of potential DCD donors to evaluate the time to death and to identify associated factors. Their results have aided planning and resourcing of DCD organ recovery and helped maximize DCD donor numbers. Pettigrew and Bradley (3) subsequently investigated the impact on donor numbers and transplant function of using instead a maximum 'cut-off' time of 4 hours. The agonal phase of 173 potential DCD donors was characterized according to the presence or absence of various factors and their impact on transplant outcome evaluated. Of referrals who became donors, 23% arrested more than one hour after withdrawal of life support, but it was shown that neither agonal phase instability nor its duration influenced transplant outcome. DCD kidney numbers could therefore be increased by 30%, without compromising transplant outcome, by lengthening the maximum waiting time after withdrawal of life support from one to four hours.

Kidneys from DCD donors have long been recognised as having great potential to address the shortfall in kidneys available for transplantation. However, there has been concern that the long-term outcome may be inferior to that from using kidneys from brain-death donors. Research led by Bradley, Watson and Pettigrew in 2009, and based on an extensive analysis of the UK registry data (4,5) showed that kidneys from DCD donors provided graft survival and function equivalent to that of grafts from brain death donors. The team also identified key determinants of graft survival in recipients of DCD kidneys. Their findings strongly supported increased use of kidneys from DCD

donors, and recommended that an allocation policy for DCD donor kidneys avoid large age mismatches, restrict the use of kidneys poorly matched for HLA in younger recipients, and minimise cold ischaemic time. Pettigrew, Watson and Bradley have similarly reported satisfactory outcomes for pancreas and liver transplants using organs from DCD donors.
A factor contributing to cold ischaemia is the "mandatory" cross match test to exclude donor specific antibodies in the potential recipient. Bradley and Watson (6), in conjunction with Dr Craig Taylor (NIHR Biomedical Research Centre) were the first to report the safety and clinical efficacy of omitting the cross-match test, when it was predicted to be negative, based on sensitization history and rigorous HLA-specific antibody screening (6). Adoption of this policy, when allowed in selected patients, was safe and effective, allowing a 2 hour reduction in cold ischaemic time which for DCD kidneys has improved transplant outcome.
Finally, Watson and Bradley (7) led a UK multicentre, randomized controlled trial showing that pre-transplant storage of DCD kidneys by cold pulsatile machine perfusion offered no advantage in transplant outcome over simple cold storage which remains cheaper and more straightforward.

3. References to the research (indicative maximum of six references)

(1) Watson CJ, Roberts R, Wright KA, Greenberg DC, Rous BA, Brown CH, Counter C, Collett D, Bradley JA. How safe is it to transplant organs from deceased donors with primary intracranial malignancy? An analysis of UK Registry data. Am J Transplant. 2010 Jun;10(6):1437-44. doi: 10.1111/j.1600-6143.2010.03130.x. Epub 2010 May 10. PMID: 20486904
(2) Suntharalingam C, Sharples L, Dudley C, Bradley JA, Watson CJ. Time to cardiac death after withdrawal of life-sustaining treatment in potential organ donors. Am J Transplant. 2009 Sep;9(9):2157-65. doi: 10.1111/j.1600-6143.2009.02758.x. Epub 2009 Jul 22. PMID: 19681825
(3) Reid AW, Harper S, Jackson CH, Wells AC, Summers DM, Gjorgjimajkoska O, Sharples LD, Bradley JA, Pettigrew GJ. Expansion of the kidney donor pool by using cardiac death donors with prolonged time to cardiorespiratory arrest. Am J Transplant. 2011 May;11(5):995-1005. doi: 10.1111/j.1600-6143.2011.03474.x. Epub 2011 Mar 30. PMID: 21449941
(4) Summers DM, Johnson RJ, Allen J, Fuggle SV, Collett D, Watson CJ, Bradley JA. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. Lancet. 2010 Oct 16;376(9749):1303-11. doi: 10.1016/S0140-6736(10)60827-6. Epub 2010 Aug 18. PMID: 20727576
(5) Summers DM, Johnson RJ, Hudson A, Collett D, Watson CJ, Bradley JA. Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study. Lancet. 2012 Dec 19. doi:pii: S0140-6736(12)61685-7. 10.1016/S0140-6736(12)61685-7. [Epub ahead of print] PMID: 23261146
(6) Taylor CJ, Kosmoliaptsis V, Sharples LD, Prezzi D, Morgan CH, Key T, Chaudhry AN, Amin I, Clatworthy MR, Butler AJ, Watson CJ, Bradley JA. Ten-year experience of selective omission of the pretransplant crossmatch test in deceased donor kidney transplantation. Transplantation. 2010 Jan 27;89(2):185-93. doi: 10.1097/TP.0b013e3181c926f2. PMID: 20098281
(7) Watson CJ, Wells AC, Roberts RJ, Akoh JA, Friend PJ, Akyol M, Calder FR, Allen JE, Jones MN, Collett D, Bradley JA. Cold machine perfusion versus static cold storage of kidneys donated after cardiac death: a UK multicenter randomized controlled trial. Am J Transplant. 2010 Sep;10(9):1991-9. doi: 10.1111/j.1600-6143.2010.03165.x. PMID: 20883534

4. Details of the impact (indicative maximum 750 words)

The research described has had a major impact on renal and other types of organ transplantation: it has helped increase access to deceased donor kidney transplantation and informed organ storage and allocation policy, locally and nationally, particularly for kidneys from circulatory death (DCD) donors.

The novel finding that organs derived from patients dying from primary intracranial malignancy, including those with high-grade tumours, posed a very small risk of tumour transmission has helped change practice in the UK and internationally. The Department of Health Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) in the UK recently (2012) published a report (1), citing the Cambridge findings as key evidence, and recommended that organs donated by donors with primary CNS cancer should generally be used for transplantation, thereby increasing access to transplantation and giving an estimated gain of 320 life-years in UK kidney transplant recipients annually (1). The Cambridge research was also instrumental in

determining international policy for transplanting organs from donors with intracranial malignancy (2).

The Cambridge study on time-to-circulatory-death after withdrawal of life sustaining treatment in potential organ donors has been recognized as the most authoritative publication on this subject. It has influenced planning and resourcing of organ recovery after cardiac death and helped maximize donor numbers locally and nationally. Extending the stand-down time after withdrawal of life supporting treatment in potential DCD donors from one to four hours has increased DCD numbers by 30% and Cambridge became in 2009/10 (and remains in 2013) the largest UK centre for DCD kidney transplantation (3, 4). This influenced practice nationally and the National Organ Retrieval Service in the UK recently increased the stand down time for potential DCD donors from two to three hours (plus a further two hours if the potential donor became unstable)(5).

In the UK the number of kidneys donated after circulatory death rose from 264 in 2008 to 674 in 2011/12 and continues to increase (6). The Cambridge-led Lancet study showing that long-term transplant outcome was equivalent in recipients of kidneys from DCD and brain death (BD) donors greatly stimulated the use of such kidneys. The article was accompanied by a complimentary editorial and initiated correspondence, a review and considerable media interest (7). While kidneys from BD donors have been shared according to a national allocation scheme, kidneys from DBD donors have not been shared nationally but used locally instead. On the basis of the two Lancet papers, which also identified the key factors influencing outcome after DCD kidney transplantation, a working party of the Kidney Advisory Group of NHSBT was established (8), and advised a national sharing scheme for kidneys from DCD donors. The second Lancet paper, showing that kidneys from DCD donors were more susceptible to cold ischaemic injury than kidneys from brain death donors, led the Kidney Advisory Group working party to recommend a regional (three regional zones) rather than full national sharing to minimise transport times of shared DCD kidneys. The Kidney Advisory Group and the policy implementation group of NHSBT fully accepted the report and a UK sharing scheme for DCD kidneys is currently being implemented

The multi-centre, randomised controlled trials led by Watson and Bradley which reported that machine perfusion offered no advantage over cold storage, which was cheaper and more straightforward, were used by NICE in preparing NICE technology appraisal guidance 165 ‘Machine perfusion systems and cold static storage of kidneys from deceased donors’. The NICE Committee took into consideration the Group’s clinical effectiveness evidence and concluded, in agreement with this evidence, that the LifePort kidney transporter could not be preferentially recommended over other forms of storage of kidneys from deceased donors (9).

Finally, the Cambridge experience which demonstrated for the first time the safety and feasibility of selective omission of the pre-transplant cross-match test to reduce cold ischaemic times during kidney transplantation was incorporated into the British Society of Histocompatibility and Immunogenetics/ British Transplantation Society Guidelines for the Detection and Characterisation of Clinically Relevant Antibodies in Allotransplantation and has had a major impact on UK practice (10).

5. Sources to corroborate the impact (indicative maximum of 10 references)

(1) Warrens A, et al., Advising potential recipients on the use of organs from donors with primary central nervous system tumours. (for the Advisory Committee on the Safety of Blood, Tissues and Organs, UK) Transplantation 2012; 93(4): 348-353

(2) Watson CJ, Bradley JA. Evaluating the risk of cancer transmission to optimize organ usage. Am J Transplant. 2011 Jun;11(6):1113-4.

(3) Reid AW, Harper S, Jackson CH, Wells AC, Summers DM, Gjorgjimajkoska O, Sharples LD, Bradley JA, Pettigrew GJ. Expansion of the Kidney Donor Pool by Using Cardiac Death Donors with Prolonged Time to Cardiorespiratory Arrest. Am J Transplant. 2011 May;11(5):995-1005

(4) NHSBT statistics on kidney transplantation. http://www.uktransplant.org.uk/ukt/statistics/transplant_activity_report/transplant_activity_report.jsp

(5) NHSBT National standards for organ retrieval from deceased donors. www.bts.org.uk/Documents/9.1.13%20Retrieval%20Standards%20Document%20v2%206%20effective%20010113.pdf

(6)http://www.organdonation.nhs.uk/statistics/transplant_activity_report/current_activity_reports/ukt/kidney_activity.pdf

(7)http://www.guardian.co.uk/society/2010/aug/19/kidney-transplant-revolution-cardiac-organs

(8)http://www.organdonation.nhs.uk/newsroom/news_releases/printTemplate.asp?releaseId=250

(9) http://guidance.nice.org.uk/TA165

(10) see BSHI and BTS Guidelines for the Detection and Characterisation of Clinically Relevant Antibodies in Allotransplantation (section 9.3.3) at:- http://www.bts.org.uk/MBR/Clinical/Guidelines/Current/Member/Clinical/Current_Guidelines.aspx