Institution: Keele University

Unit of Assessment: UoA3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Improving outcomes for people on peritoneal dialysis

Period when the underpinning research was undertaken: 2000-present

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Simon Davies	Professor of Nephrology and Dialysis Medicine Honorary Professor Honorary Senior Lecturer	2007 - present 2004 to 2007 1993 to 2004
Dr Mark Lambie	Senior Lecturer in Renal Medicine	2013 - present
Dr John Belcher	Senior Lecturer/Research Associate	2012 – 2018/2020 - present
Dr Ivonne Solis-Trapala	Senior Lecturer in Medical Statistics	2015 - present
Stephen Dent	Research User Group	n/a

Period when the claimed impact occurred: Since 2013

Is this case study continued from a case study submitted in 2014? N

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

Peritoneal Dialysis is used to treat 380,000 people with kidney failure nationally and internationally. Our research has contributed to sustained improvement in their survival in the US and Europe, almost double that seen for in-centre haemodialysis treatment. We have identified two types of peritoneal membrane injury which require different approaches to improve fluid management, while avoiding excessive harmful exposure from glucose in dialysis fluids. This has informed international guidelines for membrane assessment and improved prescription of peritoneal dialysis, including optimal time on treatment. Our findings have also indirectly contributed to increased global demand for non-glucose fluids, benefitting commercial suppliers.

2. Underpinning research (indicative maximum 500 words)

Peritoneal dialysis (PD) provides a home-based treatment choice that enables people to survive with kidney failure. For over 20 years Keele has been a world leader in PD research, demonstrating that peritoneal membrane function is associated with survival and that exposure to dialysis fluid, especially a high glucose concentration, can cause damage and reduce the ability of the membrane to remove fluid. This in turn causes overhydration of the patient which is strongly associated with reduced survival. Since 2000, a series of *cohort studies and clinical trials* led, or co-led, by Keele researchers has expanded understanding of this problem and shown how different approaches to prescribing PD can improve fluid removal and avoid membrane injury. Studies include the European Automated Peritoneal Dialysis Outcome Study (EAPOS) [3.1]; Global Fluid Study (GFS) [3.2]; Stoke PD Study [3.3]; Peritoneal Dialysis Competitive Risk Analysis For Long-Term Outcomes (PD-CRAFT) [3.4]; European Icodextrin Trial [3.5]; and UK-Shanghai Bioimpedance Trial [3.6].

Progressive damage of the peritoneal membrane by glucose is of two types: firstly, there is a longitudinal increase in the speed of small solute transfer across the membrane [3.1], which we previously showed to be an independent predictor of worse survival because it reduces fluid removal. We have now demonstrated that this is mediated by local inflammation [3.2]. Secondly, there can be disproportionate reduction in the efficiency of fluid removal by the membrane due to thickening that increases the risk of encapsulating peritoneal sclerosis [3.3]. This rare but severe complication of PD prevents the gastro-intestinal tract from working properly, causing pain and malnutrition and sometimes requiring major surgery, which has a significant mortality risk. We demonstrated that the risk of this condition is negligible for older patients with more comorbid conditions due to the competing risk of death from other causes, but for younger patients, this risk of peritoneal sclerosis over time is important [3.4].

Benefits of alternative approaches to high glucose prescription. There are three ways in which membrane injury and associated survival risk can be mitigated: *(1)* Using automated peritoneal dialysis (APD) which increases the efficiency of glucose in removing fluid [3.1]; *(2)* use of the polymer, icodextrin, as an alternative to glucose [3.1,3.5]; *(3)* avoidance of unnecessary increases in glucose to remove fluid by maintaining residual kidney function, which also keeps fluid status stable [3.6]. Use of icodextrin and APD in EAPOS [3.4], a study conducted in 21 European countries, mitigated both types of membrane injury and the mortality risk from fast membrane solute transfer was eliminated. In a trial comparing the use of glucose with icodextrin [3.5] we demonstrated that fluid reabsorption across the peritoneal membrane could be prevented when using icodextrin, improving overhydration while reducing glucose exposure of the peritoneal membrane. The UK-Shanghai trial [3.6] used bioimpedance assessment of body composition to guide and improve management of fluid status. Results showed that when residual kidney function was maintained, patients did not become overhydrated, obviating the need for increased membrane glucose exposure. Taken together, these studies provide clinicians with alternative strategies to manage fluid status, with the potential to improve survival while avoiding excessive exposure of the peritoneal membrane to glucose.

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

3.1 Davies SJ, Brown EA, Frandsen NE, Rodrigues AS, Rodriguez-Carmona A, Vychytil A, Macnamara E, Ekstrand A, Tranaeus A, Divino Filho JC, on behalf of the EAPOS group. Longitudinal membrane function in functionally anuric patients treated with APD: data from EAPOS on the effects of glucose and icodextrin prescription. *Kidney Int*, 2005;67(4):1609-15 **Citations 195**

3.2 Lambie M, Chess J, Donovan KL, Kim YL, Do JY, Lee HB, Noh H, Williams PF, Williams AJ, Davison S, Dorval M, Summers A, Williams JD, Bankart J, Davies SJ, Topley NT on behalf of the Global Fluid Study Investigators. Independent effects of systemic and peritoneal inflammation on peritoneal dialysis survival. *Journal Am Soc Nephrol,* 2013;24(12):2071-80 **Global Fluid Study, Citations 118**

3.3 Lambie M, John B, Mushahar L, Huckvale K, Davies SJ. The peritoneal osmotic conductance is low well before the diagnosis of encapsulating peritoneal sclerosis in made. *Kidney International 2010*;28(6):611-618. **Stoke PD Study: Citations 94**

3.4 Lambie M, Teece L, Johnson D, Petrie M, Mactier R, Solis-Trapala I, Belcher J, Bekker H, Wilkie M, Tupling K, Phillips-Darby, Davies, SJ. Estimating Risk of Encapsulating Sclerosis Accounting for Competing Risk of Death: Nephrology Dialysis Transplantation 2019:34(9);1585-91 **PD-CRAFT, Citations 5**

3.5 Davies, S. J., Woodrow, G., Donovan, K. Plum, J., Williams, P., Johansson, A. C., Bosselmann, H. P., Heimburger, O., Simonsen, O., Davenport, A., Tranaeus, A., and Divino Filho, J. C. Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. *J Am Soc Nephrol* 2003; 14:2338-44. **European Icodextrin Study, Citations: 347**

3.6 Tan BK, Yu Z, Fang W, Lin A, Ni Z, Qian J, Woodrow G, Jenkins S, Wilkie M, Davies SJ Longitudinal bioimpedance vector plots add little value to fluid management of peritoneal dialysis patients. Results of the UK-Shanghai BIA trial Kidney Int; 2015;89(2):487-97 UK**-Shanghai Study, Citations: 30**

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

Evidence of a relative and sustained improvement in survival on peritoneal dialysis compared to haemodialysis since research was published

Survival analyses from the US Renal Data System [5.1a] show that "adjusted all-cause mortality in prevalent patients receiving hemodialysis decreased from 192.9 per thousand in patient-years in 2009 to 164.6 in 2018. The decrease was even greater in patients receiving PD, in whom the mortality rate decreased from 164.2 to 131.5. Median survival among incident hemodialysis patients improved from approximately 37 months in 2003 to 42 months 2008 and to 47 months in 2013 **(Figure 5.7)** [5.1a]**.** The improvement was even greater for patients initiating PD".

In 2016, the European Renal Registry reported on sequential cohorts starting dialysis in which survival used to be equivalent for these different types of dialysis, but progressively has been disproportionately better for those treated with PD [5.1b]. The authors of this publication argue this was not due to changes in patient selection, suggesting that improvement in survival on PD, amongst other things, is likely to reflect better fluid management, appreciation of the value of residual kidney function and the greater importance of fluid versus solute removal. Research at Keele has focussed primarily on these issues and we have consistently shown that peritoneal membrane function, which is crucial to fluid removal, predicts survival [3.2]. This early survival benefit for PD is still evident in the most recent annual European Registry report (2018, **Figure A.5.1**) [5.1c].

How our research has influenced guidance on peritoneal dialysis prescription

Evidence-based guidance on dialysis prescription worldwide is led by the International Society of Peritoneal Dialysis (ISPD). Their regular publications of guidelines are highly cited, downloaded and viewed [5.2]. Our research is well represented in the most recent, as well as previous, iterations of this guidance, including prescribing high-quality PD [5.2] for people with cardiovascular disease, guidance on how long patients should remain on peritoneal dialysis [5.3] and, most recently, the evaluation of peritoneal membrane function [5.4]. Specifically, our research has contributed to this guidance in the following ways:

(a) Our research on membrane function [3.1; 3.2; 3.3] informed a new framework for classifying types of membrane dysfunction and recommendations on how membrane function is evaluated in the clinic [5.4]; the avoidance of excessive use of high glucose concentrations [3.1; 3.3] (and replacement with icodextrin if available) [5.2; 5.2; 5.4]; and how to assess the risk of encapsulating peritoneal sclerosis [3.2; 3.3; 3.4 – data used by the guideline committee and published subsequently] taking competing risks into account [5.3].

(b) Use of icodextrin to improve ultrafiltration: our trial [3.5] - the first to show that icodextrin improves fluid removal and hydration status in people with fast membrane solute transfer - is included in all systematic reviews of trial evidence [5.5 (Cochrane Review); 5.6, "Our systematic review demonstrates substantial clinical benefits for icodextrin based on high level evidence",] used to underpin the ISPD guidelines [5.2; 5.4].

(c) The value of residual kidney function in maintaining stable fluid status was demonstrated in our trial [3.6], the only longitudinal study linking these parameters [5.2]

Evidence this guidance has impact through adopted practice and patient benefit

(a) The use of *automated peritoneal dialysis* to mitigate the mortality risk in patients with fast membrane transport, a strategy that follows directly from our research, was associated with a partial reduction in mortality and hospitalisation risk in a study of >10,000 patients treated by a Large Dialysis Organisation, (Davita, based in the US) [5.7].

(b) A report of data from the international Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) shows that across the world *icodextrin* is preferentially prescribed in people with fast membrane solute transport. This has also translated into less use of high glucose concentrations and a maintenance of equivalent fluid removal [5.8]

Supporting shared decision making

Funded by Kidney Research UK and in collaboration with Hilary Bekker (Professor of Medical Decision Making at Leeds University), we have ensured that our research supports shared decision making through the development of a Dialysis Decision Aid, first made available in 2015 and recently updated. This decision aid, developed in collaboration with nurses and patients, including those at our affiliated clinical unit (University Hospital of North Staffordshire), supports patients in choosing the type of dialysis they will have, and the choice between home and hospital-based treatments. Used in 1/3 of kidney units, the tool is also available to patients on the Kidney Research UK website [5.9] (typically 600 patient downloads per year). It is endorsed by NICE, European Best Practice Group, quality tested by the International Decision Aid Library Inventory System and included as an online decision aid on https://www.thinkkidneys.nhs.uk/ckd/tools-for-change/patient-decision-aids/ and international Med-Decs https://www.med-decs.org/en/kidney-failure websites. It has also been translated into Spanish (by the Spanish Society of Nephrology) and Italian (by the Italian Association of Kidney Patients). Incorporated in the Dialysis Decision Aid is information derived from our research on the risk of developing encapsulating peritoneal sclerosis, which is extremely low for older patients [3.4].

Impact on industry

Baxter HealthCare, the largest global company producing PD solutions and the exclusive manufacturer of icodextrin (commercially called *Extraneal*) have used our research to demonstrate the added clinical value of this product. They have now obtained licences for its use across the world [5.10].

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

[5.1] Sustained improvement in mortality on peritoneal dialysis relative to haemodialysis.
(a) US Renal Data System (data up to 2018), https://adr.usrds.org/2020/end-stage-renal-disease/5-mortality Figure 5.7
and (b) Trends in dialysis modality choice and related patient survival in the ERA-EDTA Registry over a 20-year period, NDT, 31:2016 https://doi.org/10.1093/ndt/gfv295
and (c) ERA-EDTA Annual Report 2018, Page 33, Figure A.5.1 https://www.era-edta.org/registry/AnnRep2018.pdf

[5.2] Testimonial of Adoption of Intenational Summary of Guidelines (Editor, Peritoneal Dialysis International) Dec 2020.
ISPD prescription guidelines. Prescribing High Quality Goal-Orientated Peritoneal Dialysis (The over-arching guideline paper). Brown EA, Blake PG, Boudville N, Davies S, De Arteaga J, Dong J, Finkelstein F, Foo M, Hurst H, Johnson DW, Johnson M, Liew A, Moraes T, Perl J, Shroff R, Teitelbaum I, Wang AY, Warady B. *International Society for Peritoneal Dialysis practice recommendations: Prescribing high-quality goal-directed peritoneal dialysis.* Perit Dial Int. 2020 Jan 21:896860819895364. DOI: 10.1177/0896860819895364
Underpinning evidence - Wang AY, Dong J, Xu X, Davies S. *Volume management as a key dimension of a high-quality PD prescription* Perit Dial Int. 2020;40(3):282-292 DOI: 10.1177/0896860819895365 And also, see guideline 2.2.3 in Wang AY, Brimble KS, Brunier G, Holt SG, Jha V, Johnson DW, Kang SW, Kooman JP, Lambie M, McIntyre C, Mehrotra R, Pecoits-Filho R. ISPD *Cardiovascular and Metabolic Guidelines in Adult Peritoneal Dialysis Patients Part I - Assessment and Management of Various Cardiovascular Risk Factors.* Perit Dial Int. 2015 Jul-Aug;35(4):379-87. DOI: 10.3747/pdi.2014.00279. PMID: 26228782; PMCID: PMC4520720

[5.3] ***International Society of Peritoneal Dialysis guidance on how long a patient should remain on peritoneal dialysis*** *without risking membrane injury and encapsulating peritoneal sclerosis. In this guideline 8/104 of the references are from our research – more than any other*

single group. See references 83, 89 and highlighted text describing PD-CRAFT study findings prior to publication. Brown EA, Bargman J, van Biesen W, Chang MY, Finkelstein FO, Hurst H, Johnson DW, Kawanishi H, Lambie M, de Moraes TP, Morelle J, Woodrow G. Length of Time on Peritoneal Dialysis and Encapsulating Peritoneal Sclerosis - Position Paper for ISPD: 2017 Update. Perit Dial Int. 2017 Jul-Aug;37(4):362-374. DOI:10.3747/pdi.2017.00018

[5.4] ***ISPD Recommendations for the evaluation of peritoneal membrane dysfunction in adults****: classification, measurement, interpretation and rationale for intervention* Johann Morelle, Joanna Stachowska-Pietka, Carl Öberg, Liliana Gadola, Vincenzo La Milia, Zanzhe Yu, Mark Lambie,[7] Raj Mehrotra, Javier de Arteaga, Simon Davies DOI: 10.1177/0896860820982218

[5.5] Use of icodextrin to improve ultrafiltration. ***Systematic Review of Evidence*** Htay H, Johnson DW, Wiggins KJ, Badve SV, Craig JC, Strippoli GF, Cho Y. Biocompatible dialysis fluids for peritoneal dialysis. Cochrane Database Syst Rev. 2018 Oct 26;10:CD007554 DOI: 10.1002/14651858.CD007554.pub3.

[5.6] Goossen K, Becker M, Marshall MR, et al. **Icodextrin Versus Glucose Solutions for the Once-Daily Long Dwell in Peritoneal Dialysis**: An Enriched Systematic Review and Meta-analysis of Randomized Controlled Trials. *Am J Kidney Dis*. 2020;75(6):830-846. DOI: 10.1053/j.ajkd.2019.10.004

[5.7] Mehrotra R, Ravel V, Streja E, Kuttykrishnan S, Adams SV, Katz R, Molnar MZ, Kalantar-Zadeh K. Peritoneal Equilibration Test and Patient Outcomes. Clin J Am Soc Nephrol. 2015 Nov 6;10(11):1990-2001. doi: 10.2215/CJN.03470315 **This large cohort study confirms the detrimental effect of high solute transport membrane function on survival and demonstrates the mitigating effect of using Automated Peritoneal Dialysis.**

[5.8] Analysis of Icodextrin prescribing practice from the International Peritoneal Dialysis Outcomes and Practice Patterns Study. Report from Arbor Research Collaborative for Health on the Data from the International PDOPPS study that shows that across the world icodextrin is preferentially prescribed in people with fast membrane solute transport.

[5.9] *Dialysis Decision Aid.* https://www.kidneyresearchuk.org/DialysisDecisionAid See page 45 reference 12 and page 48 reference Lambie and Davies as research team.

[5.10] Evidence that there has been, since 2000, a sustained increase in the use of APD and uptake of icodextrin use in countries where this is available. (Testimonial, Baxter HealthCare).