Institution: Keele University

Unit of Assessment: UoA3

Title of case study:
Improving clinical outcomes of patients with kidney failure treated by peritoneal dialysis

1. Summary of the impact

Peritoneal dialysis (PD) is used to treat kidney failure in 250,000 individuals worldwide, a figure growing at 20% per annum in developing economies. Critical to this therapy is the removal of adequate salt, water and uraemic toxins by the peritoneal membrane. Our research has shown how variability in peritoneal membrane function impacts on clinical outcomes, how the treatment itself affects this function over time and how the design of dialysis solutions can improve membrane performance. This knowledge has informed changes in dialysis prescription practice and fluid design contributing to the sustained improvement in patient outcomes observed over the last 20 years.

2. Underpinning research

The research comprises **observational cohort**, **interventional** and **mechanistic** studies undertaken by and led from Keele University under the direction of Professor Davies since 1990.

The **Stoke PD cohort study**, now running for 22 years was conceived to answer two inter-related questions: how does membrane function affect patient outcomes and how does dialysis affect the membrane? It is the largest single centre study of longitudinal peritoneal membrane function, with >800 patients with detailed phenotypic description providing the first accurate account of long-term PD treatment [1]. It has formed the template for subsequent multi-centre multi-national cohorts including the **European Automated Peritoneal Dialysis Outcomes Study (EAPOS)** and the **Global Fluid Study**. Key insights, all first described in this cohort but subsequently corroborated include:

1. Demonstration that individual variation in membrane function (rate of solute transport) affects survival, independent of residual kidney function and comorbidity. Rapid solute transport, initially thought to be a benefit in clearing uremic toxins, was shown to be detrimental as it leads to more rapid loss of the osmotic gradient required to achieve ultrafiltration and more rapid fluid reabsorption. [1,2]
2. Evidence that membrane function changes with time on treatment and that this is influenced by prior glucose prescription, severity of peritoneal infection episodes and earlier loss of residual kidney function.[3]
3. Evidence that at least two types of membrane injury occur with time on treatment – initially an increase in solute transport rate – followed by a more serious reduction in the ultrafiltration capacity of the membrane in long-term patients. [4]

These observations were extended by **EAPOS** (2000-2003), co-led by Davies and Prof Brown (Imperial College) incorporating anuric PD patients recruited from 14 European countries, in which:

1. The adverse effects of high membrane solute transport rate described above in continuous ambulatory peritoneal dialysis (CAPD – 4 manual exchanges per day) were shown to be abrogated by the use of automated peritoneal dialysis (APD, enables multiple exchanges to be given overnight) thus identifying one of the key benefits of this modification of therapy [5]
2. Confirmation of the detrimental effects of glucose exposure as a driver for membrane injury and conversely the protective effects of the glucose-free polymer, icodextrin. [6]
3. Demonstration of a minimum achieved daily ultrafiltration volume for survival in patients with complete loss of urine output. [5]

Davies was also chief investigator for the **multicentre Phase 4 investigator-led European Icodextrin study**, (2000-2002, 10 centres in UK, Sweden, Germany), designed to show that this glucose polymer not only improved fluid removal in patients whose membrane characteristics are

associated with worse outcomes because of rapid glucose absorption, but that its use led to a sustained improvement in hydration status [7].

Mechanistic studies undertaken by the group using isotopic labelling of albumin and water have tested predictions of the main theory (3 pore model) describing peritoneal membrane function as developed by Professor Rippe, Lund University Sweden. Clinical validation has confirmed the mechanism of fluid reabsorption, the main pathways of fluid transport and factors contributing to sodium removal (convection, diffusion and reabsorption) [8]. These studies in humans have underpinned the need for and design of potential low sodium solutions, in collaboration with industry to improve the diffusive component of sodium removal with the purpose of further improving fluid management and blood pressure control.

3. References to the research

This research began at Keele in 1990 and by 1998 it was apparent that membrane function predicts survival. Since then Davies has been asked to deliver regular key-note lectures describing our findings at the International Society of Peritoneal Dialysis, EuroPD and American Society of Nephrology. In 2003 Davies was invited to chair the EuroPD scientific committee and the ISPD international research committee until he took up the presidency of the society in 2010. The research has led to 10 book chapters and ~100 journal publications (>3000 citations).

1. DAVIES, S.J., L. PHILLIPS, A. GRIFFITHS, L. RUSSELL, P.F. NAISH AND G.I. RUSSELL. (1998) What really happens to patients on long-term peritoneal dialysis? *Kidney International.* 54(6):pp.2207-2217 DOI: **10.1046/j.1523-1755.1998.00180.x 216 citations**
2. DAVIES, S. J., L. PHILLIPS, AND G. I. RUSSELL. (1998). Peritoneal solute transport predicts survival on CAPD independently of residual renal function. *Nephrology Dialysis Transplantation* 13(4):962-968 DOI: **10.1093/ndt/13.4.962 146 citations**
3. **§**DAVIES, S.J., L. PHILLIPS, P.F. NAISH, G.I. RUSSELL. (2001) Peritoneal glucose exposure and changes in membrane solute transport with time on Peritoneal Dialysis. *Journal American Society of Nephrology* 12(5):pp.1046-1051 **192 citations**
4. DAVIES SJ: (2004) Longitudinal relationship between solute transport and ultrafiltration capacity in peritoneal dialysis patients. *Kidney Int*; 66(6):2437-45. **76 citations**
5. **§**BROWN EA, DAVIES SJ, RUTHERFORD P, MEEUS F, BORRAS M, RIEGEL W, DIVINO FILHO JC, VONESH E, VAN BREE M: Survival of Functionally Anuric Patients on Automated Peritoneal Dialysis: The European APD Outcome Study. *J Am Soc Nephrol* 2003;14:2948-57 DOI:**10.1097/01.ASN.0000092146.67909.E2 185 citations**
6. 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 (2005). Longitudinal membrane function in functionally anuric patients treated with APD: data from EAPOS on the effects of glucose and icodextrin prescription. *Kidney Int*, 67(4):1609-15 DOI: **10.1111/j.1523-1755.2005.00243.x 85 citations**
7. 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. (2003) Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. *J Am Soc Nephrol* 14: 2338-44 DOI: **10.1097/01.ASN.0000083904.12234.27 176 citations**
8. ASGHAR, R AND DAVIES SJ. (2008) Pathways of fluid transport and reabsorption across the peritoneal membrane. *Kidney Int,* 73(9):1048-53

§ Two of the 10 most significant publications in Peritoneal Dialysis (see Section 5 reference [4]).

Research Funding:
2001-3 Bi-directional Water Flow across the dialysed peritoneum. £95,000 Kidney Research UK (First dialysis study ever funded by KRUK)
2000-2003 EAPOS Study: Funding of data coordinator. Baxter Healthcare (Europe)
2000-2002: Icodextrin Phase 4 study. Baxter Healthcare, (Europe)

1990-2000: Research Assistant North Staffordshire Medical Institute Funded ~ £250,000

4. Details of the impact

Since the early 1990s the mortality rates for peritoneal dialysis patients have almost halved (from ~400 to ~200 deaths/1000 patient years at risk) [1]; mortality used to be almost double that for haemodialysis patients but in the last few years these two dialysis modalities are equivalent in efficacy over 5 years with early survival advantages for PD in several national registries. This dramatic improvement is undoubtedly multifactorial but is coincident with the clearer understanding of what is meant by adequate treatment and how the peritoneal membrane function in particular influences survival. The contribution made by the Keele research group is widely acknowledged: examples of this include the award made in 2013 by the American National Kidney Foundation (NKF) to Davies of their International Distinguished Medal [2], by the International Society of Peritoneal Dialysis who elected Davies president 2010-12 and published a supplement on the UK contribution to the therapy in their journal [3] and a recent book describing 'Landmark Papers in Nephrology' [4].

1. Changing the paradigm of what is considered adequate dialysis: In 1997 the NKF's Kidney Disease Outcomes and Quality Initiative (KDOQI) published guidelines stating that patients failing to achieve a specified small solute clearance target should not stay in peritoneal dialysis; given that this target was more easily achieved in patients with rapid peritoneal solute transport the expectation was that these patients should fare best on PD. This was refuted by our demonstration that rapid solute transport was associated with worse outcomes in peritoneal dialysis, an observation corroborated by others including the Canada-USA study and the Australian/New Zealand registry, and subsequently in a meta-analysis published in 2006 [5] which concluded that in patients treated with continuous ambulatory peritoneal dialysis (CAPD) high transport was associated with worse survival. This led to paradigm shift in what was considered adequate dialysis away from the view that it could be defined simply in terms of solute clearance. In particular it led to an equal focus on fluid management and to the advice that membrane characteristics should be taken into account and clearance targets modified [6]. EAPOS extended the evidence base and it is now accepted that the use of APD and icodextrin in patients with high transport characteristics mitigates their survival disadvantage and that anuric patients unable to achieve a daily ultrafiltration target of 0.75-1.00 litre should be transferred to haemodialysis. These changes in emphasis of what is meant my adequate peritoneal dialysis are evident in current clinical KDOQI and European Best Practice Guidelines which now include fluid management as a key component of adequate treatment [6,7].

3. Progressive membrane injury. The demonstration that peritoneal dialysis fluids high in glucose and their associated glucose degradation products (GDPs), generated by the sterilisation procedure, drive progressive membrane injury has provided a strong clinical argument for the development of more bio-compatible (low GDP solutions) by the leading dialysis fluid manufacturing companies [8,9]. A recent randomised controlled trial has shown that a low GDP solution prevents the early changes in membrane function in comparison to conventional glucose solutions [10]. Our research has also had significant economic impact. The peritoneal dialysis fluid manufacturing market was valued at $1.7 billion in 2008 and is expected to grow at 7% per annum to reach $2.9 billion in 2015. The clinical justification for using premium fluids such as the glucose polymer icodextrin and biocompatible solutions is underpinned by our observations.

4. Modelling membrane injury. The longitudinal membrane changes we have described include dissociation between increasing solute transport and reduction in the efficiency of fluid transport. This has led the authors of the three pore model, a mathematical description of membrane function to modify their model by accounting for interstitial fibrosis and underpinned the arguments for monitoring membrane function on PD patients [7].

5. Designing and testing a novel low sodium dialysis solution. As a direct consequence of our work on peritoneal ultrafiltration, validation of the three pore membrane model and evidence of over-hydration (salt retention) in PD patients, Gambro (now taken over by Fresenius) have developed a

low sodium dialysis solution. Following the pilot study (led from Keele in collaboration with Lund University, Sweden) Fresenius is now conducting a multi-centre European Phase 3 evaluation of the effect of this solution in improving blood pressure [9].

5. Sources to corroborate the impact

1. ***US Renal Data system 2010: see Figure 6.1 Adjusted mortality rates, by modality &year of treatment:*** http://www.usrds.org/2010/view/v2_06.asp

2. ***American National Kidney Foundation Award 2013: International Distinguished Medal*** http://www.kidney.org/news/meetings/clinical/recognition/medalRecipients.cfm

3. Article describing the contribution made by the Keele Peritoneal Dialysis Research Group in the International Society of Peritoneal Dialysis' journal.
The Stoke contribution to peritoneal dialysis research. Wilkie ME and Jenkins SB. Perit Dial Int. 2011 Mar;31 Suppl 2:S43-8 www.ncbi.nlm.nih.gov/pubmed/21364207

4. Two of the most significant 10 papers ever published in the field of peritoneal dialysis were identified in this book describing the 200 most influential publications since 1842.
Landmark Papers in Nephrology, Ed: John Feehally, Christopher McIntyre and J Stewart Cameron Oxford University Press, 2013
https://www.google.co.uk/#q=Nephrology+most+significant+papers+Cameron+Feehally

5. Meta-analysis corroborating the impact of membrane transport on survival of PD patients.
Brimble KS, Walker M, Margetts PJ, Kundhal KK, Rabbat CG. Meta-analysis: peritoneal membrane transport, mortality, and technique failure in peritoneal dialysis. J Am Soc Nephrol. 2006 Sep;17(9):2591-8

6. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for 2006 Updates: Hemodialysis Adequacy, Peritoneal Dialysis Adequacy and Vascular Access. Am J Kidney Dis 48:S1-S322, 2006 (suppl 1)
https://www.kidney.org/professionals/kdoqi/guideline_upHD_PD_VA/pdf/pd_guidelines_complete.pdf

7. European Best Practice Guidelines: Adequacy of Peritoneal Dialysis Nephrol Dial Transplant (2005) 20 [Suppl 9]: ix24–ix27 http://ndt.oxfordjournals.org/content/20/suppl_9.toc
and Evaluation of peritoneal membrane characteristics: a clinical advicefor prescription management by the ERBP working group. Nephrol Dial Transplant (2010) 25: 2052–2062
http://ndt.oxfordjournals.org/content/early/2010/03/04/ndt.gfq100.full.pdf

8. Personal communication (available on request) from Medical Director (Renal) – Europe, Middle East and Africa Baxter Healthcare SA.

9. Individual corroboration from Marketing Director Home Therapies, International Marketing and Medicine, Fresenius Medical Care Deutschland GmbH.

10. Trial demonstrating reduced longitudinal membrane function change with PD solution designed to minimise the detrimental effects of glucose exposure.
The effect of low glucose degradation product, neutral pH versus standard peritoneal dialysis solutions on peritoneal membrane function: the balANZ trial. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, Jones B,Kulkarni H, Langham R, Ranganathan D, Schollum J, Suranyi MG, Tan SH, Voss D; on behalf of the balANZ Trial Investigators. *Nephrol Dial Transplant. 2012 Dec;27(12):4445-53* www.ncbi.nlm.nih.gov/pubmed/22859794