Peritoneal Dialysis in Scotland: An analysis of complications and outcomes in a contemporary national cohort.

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Abstract

Peritoneal dialysis (PD) utilisation is falling in Western Countries. Concerns regarding reduced survival on PD, impact of inadequate dialysis on patient outcomes and the serious complication of encapsulating peritoneal sclerosis (EPS) may be contributing to the decline of PD. The exact incidence of EPS has been difficult to establish because of differences in design of published studies. In Scotland there was concern that the incidence of EPS was increasing, which prompted discussions about the future role and risks of PD. The aim of the MD was to establish an accurate incidence of EPS in Scotland and to examine complications and outcomes of PD patients to try to answer the question of who and for how long PD should be used in our population. Since 1999 all adult renal units in Scotland have completed a PD Audit form 6 monthly for every PD patient which gives details of PD population, source of new patients, reasons for stopping PD, causes of technique failure, details of all peritonitis episodes, adequacy test results and basic laboratory results. This prospectively collected data was linked to further demographic and laboratory data from the Scottish Renal Registry database for analysis. The analysis focussed on all incident patients commencing PD between 1st January 2000 and 31st December 2007 (n=1324), with follow-up to 30th June 2011. Our data analysis confirmed the ongoing fall in PD population in Scotland, and greater usage of APD. Peritonitis rates have remained steady at 1 episode every 19.9 months when averaged over the study period; similar to UK and Australasian results but worse than North American centres. Several risk factors for peritonitis were identified in our population including unit, CAPD compared to APD, diabetes mellitus (DM) in females, older age, hypoalbuminaemia, and lower residual renal function (RRF) at the start of PD. We established that the overall risk of EPS is low, but if PD is continued beyond 4 years the risk is substantial at 1 in 13 patients, with an exponentially increasing incidence with longer PD exposure. Survival is poor with 46.8% mortality at 1 year after diagnosis. No clear risk factors were apparent other than PD exposure. Analysis of patient survival identified several factors associated with poorer survival including increasing age, hypoalbuminaemia and RRF at the start of PD, presence of DM and multisystem primary renal diagnoses as well as having experienced peritonitis. The main causes of technique failure in our cohort include peritonitis (42.9%) and inadequate dialysis (22.1%). Predictors of technique failure include DM, lower RRF at the start of PD and being treated in more recent PD eras. Overall analysis of the PD cohort has shown that PD is a short-term treatment in Scotland with only a quarter of patients continuing PD beyond 3 years, with the remainder stopping for a transplant, technique failure or death. It is not possible to predict how long an individual patient will continue PD, but certain patients have poorer outcomes including the elderly (>70 years), those with DM and those hypoalbuminaemic at the start of PD. Therefore the actual number of patients who will continue PD long enough to be at significant risk of EPS is very small, and we believe the potential risk of EPS should not prevent patients from being offered PD in the first instance. Although some patients fare better on PD than others, we cannot state that any specific patient group should not be offered PD on the basis of our analyses particularly as we cannot show that they would have improved outcomes on haemodialysis. For the minority of patients with ongoing technique success at 4 years we suggest discussing ongoing PD, ensuring patients are informed about the EPS risk and a risk:benefit assessment of ongoing treatment should be decided on a case by case basis. It is likely that clinician attitude are driving the decline of PD, in the absence of evidence to show inferior outcomes on PD compared to HD. There would be an argument for actively increasing PD utilisation in Scotland, particularly among the elderly by expanding the assisted PD programs. Similarly, unless efforts are made to ensure adequate PD training and experience for nephrology trainees it is likely that PD will continue to decline.

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List of Abbreviations

APD	automated peritoneal dialysis
BMI	body mass index
CAPD	continuous ambulatory peritoneal dialysis
CCPD	continuous cycling peritoneal dialysis
CI	95% confidence intervals
CNS	coagulase negative staphylococcal aureus
CSN	Canadian Society of Nephrology
DM	diabetes mellitus
EPS	encapsulating peritoneal dialysis
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ESBL	Extended-spectrum beta-lactamases
g/dl	grams per decilitre
g/l	grams per litre
GDPs	glucose degredation products
HD	Haemodialysis
IP	intra-peritoneal
IPD	intermittent peritoneal dialysis
ISPD	International Society for Peritoneal Dialysis
l/wk	litres per week
MRSA	methicillin resistant staphlococcus aureus
NHS	National Health Service

List of Abbreviations

NPV	negative predictive value
PD	peritoneal dialysis
PET	peritoneal equilibration test
PMP	per million population
PO	per oral
PPV	positive predictive value
PRD	Primary renal diagnosis
prev	prevalence
RA	Renal Association
RC	renal clearance
RRF	residual renal function
SA	staphlococcus aureus
SD	Standard deviation
sens	sensitivity
SIMD	Scottish Index of Multiple Deprivation
spec	specificity
SRA	Scottish Renal Association
SRR	Scottish Renal Registry
TC	total clearance
UKRR	UK renal registry
USRDS	United States Renal Data System
WCC	white cell count
yrs	years

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My husband and family for their patience and practical support to allow me the time to complete this despite the demands of our young child and having another baby in time for the viva!

Author's Declaration

The work presented in this MD thesis was performed solely by the author, including all statistical analyses unless otherwise stated.

I declare that this thesis has been composed by myself and is a record of work performed by myself. It has not previously been submitted for a higher degree. Parts of this thesis have been presented at local and international meetings and published in peer-reviewed journals as listed separately.

Michaela Catherine Brown, July 2012.

List of Publications Relating to this Thesis

Brown MC, McManus SK, Mactier RA. Residual renal clearance in predicting dialysis adequacy. *British Journal of Renal Medicine*. 2012;17(1):9-13.

Mactier RA, Brown MC. A prospective national audit of encapsulating peritoneal sclerosis 2000-2009. Book Chapter in *Peritoneal Dialysis*, Intech 2011: ISBN 978-953-307-390-3.

Brown MC, Kerssons JJ, Mactier RA. Peritoneal dialysis-associated peritonitis rates and outcomes in a national cohort are not improving in the post millennium (2000-2007). *Peritoneal Dialysis International* 2011;31:639-650.

Brown MC, Simpson K, Kerssens JJ, Mactier RA on behalf of the Scottish Renal Registry. Encapsulating Peritoneal Sclerosis in the New Millennium: A National Cohort Study. *Clinical Journal of the American Society of Nephrol*ogy 2009;4(7):1222-9.

Brown MC, Mactier RA. Concerns regarding routine use of sodium hypochlorite for exit-site care -- what about the risks of encapsulating peritoneal sclerosis? (letter) *Peritoneal Dialysis International 2010;30(4):480.*

Summary

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The aim of the MD was to establish an accurate incidence of EPS in Scotland and to examine complications and outcomes of PD patients to try to answer the question of who and for how long PD should be used in our population.

Since 1999 all adult renal units in Scotland have completed a PD Audit form 6 monthly for every PD patient which gives details of PD population, source of new patients, reasons for stopping PD, causes of technique failure, details of all peritonitis episodes, adequacy test results and basic laboratory results. This prospectively collected data was linked to further demographic and laboratory data from the Scottish Renal Registry database for analysis. The analysis focussed on all incident patients commencing PD between 1st January 2000 and 31st December 2007 (n=1324), with follow-up to 30th June 2011.

Our data analysis confirmed the ongoing fall in PD population in Scotland, and greater usage of APD. Peritonitis rates have remained steady at 1 episode every 19.9 months when averaged over the study period; similar to UK and Australasian results but worse than North American centres.

Summary

Several risk factors for peritonitis were identified in our population including unit, CAPD compared to APD, diabetes mellitus (DM) in females, older age, hypoalbuminaemia, and lower residual renal function (RRF) at the start of PD.

We established that the overall risk of EPS is low, but if PD is continued beyond 4 years the risk is substantial at 1 in 13 patients, with an exponentially increasing incidence with longer PD exposure. Survival is poor with 46.8% mortality at 1 year after diagnosis. No clear risk factors were apparent other than PD exposure.

Analysis of patient survival identified several factors associated with poorer survival including increasing age, hypoalbuminaemia and RRF at the start of PD, presence of DM and multisystem primary renal diagnoses as well as having experienced peritonitis. The main causes of technique failure in our cohort include peritonitis (42.9%) and inadequate dialysis (22.1%). Predictors of technique failure include DM, lower RRF at the start of PD and being treated in more recent PD eras.

Overall analysis of the PD cohort has shown that PD is a short-term treatment in Scotland with only a quarter of patients continuing PD beyond 3 years, with the remainder stopping for a transplant, technique failure or death. It is not possible to predict how long an individual patient will continue PD, but certain patients have poorer outcomes including the elderly (>70 years), those with DM and those hypoalbuminaemic at the start of PD.

Therefore the actual number of patients who will continue PD long enough to be at significant risk of EPS is very small, and we believe the potential risk of EPS should not prevent patients from being offered PD in the first instance. Although some patients fare better on PD than others, we cannot state that any specific patient group should not be

offered PD on the basis of our analyses particularly as we cannot show that they would have improved outcomes on haemodialysis.

For the minority of patients with ongoing technique success at 4 years we would suggest discussing ongoing PD, ensuring patients are informed about the risk of EPS and a risk:benefit assessment of ongoing treatment should be decided on a case by case basis.

It is likely that clinician attitude and experiences are driving the decline of PD, in the absence of evidence to show inferior outcomes on PD compared to HD. There would be an argument for actively increasing PD utilisation in Scotland, particularly among the elderly by expanding the assisted PD programs. Similarly, unless efforts are made to ensure adequate PD training and experience for nephrology trainees it seems likely that PD will continue to decline inexorably.

Chapter 1

Introduction

1. Introduction

This thesis examines the major complications and outcomes for patients on peritoneal dialysis (PD). Rather than presenting exhaustive review covering all aspects of the PD literature relating to this thesis in a single introduction chapter, for clarity the individual chapters contain an introduction detailing the background and current evidence relevant to that chapter. This brief introduction chapter serves as an overview of the history and practice of PD, the major complications and outcomes of PD, highlighting important issues with current published evidence, and identifying the areas of uncertainty in the literature that this thesis aims to examine.

1.1 History of Peritoneal Dialysis

Peritoneal dialysis (PD) as a treatment for renal failure was used before haemodialysis (HD) in 1923 but the difficulties gaining access to the peritoneal cavity and the ensuing infective complications effectively arrested further development of this technique. In the late 1940s PD was used to treat an anuric patient who survived and the case-report renewed interest in PD as a potential treatment (1).

By the late 1960s intermittent PD (IPD) was being used, but not widely so. Patients would attend the hospital once or twice a week, a new catheter inserted into their peritoneal cavity each time. Initial attempts at designing indwelling catheters were unsuccessful because of infectious complications. Eventually Tenckhoff designed an indwelling catheter with cuffs that reduced the infection risk and PD became a more widespread, long-term treatment (2).

It was not until the late 1970s that the option of continuous ambulatory peritoneal dialysis (CAPD) was described, whereby patients continually had PD fluid in their abdomen (3). However it was complicated by the high peritonitis rate (1 episode every 3-4 months),

mainly because the technique involved spiking glass bottles of PD fluid up to 5 times per day. This lead to the production of PD fluid in plastic bags that could remain attached to the patient for the full dwell time and be used to drain the PD fluid into at the end without requiring a further connect procedure. The peritonitis rate duly fell to 1 episode every 11-12 months (4). Further improvement in the form of Y-tube connection improved peritonitis rates further to 1 episode every 30-35 months(5). The latest refinement incorporates "flush-before-fill" technique whereby a small amount of PD fluid is flushed through the tubing before instilling the fluid in to the patient's peritoneal cavity, effectively washing out bacteria before they can be washed into the patient (6).

Automated PD (APD), also known as continuous cycling PD (CCPD) was the next development. It had been devised in the 1960s but required a 40 litre container of fluid which was impractical so it was not until 1980 when an improved technique requiring just 10-15 litre bags allowed PD to become a useable option. APD employs a programmable machine that controls the volume, filling, dwell time and drainage of fluid whilst the patient sleeps. It requires one connect and one disconnection procedure (unless a day time exchange is also used) compared to at least 4 connects/4 disconnects for CAPD. Amongst other advantages, as the patient is supine during the dwells there is scope to increase dwell volumes, and thus dialysis, which might not otherwise be tolerated during the day. The regime, volume of fluid, duration of each dwell, number of exchanges and requirement for day time exchanges will be determined by the patient's dialysis requirements.

Different patients have differing peritoneal characteristics and need individualised PD regimes. The "transporter status" of a patient's peritoneum refers to how it behaves with respect to small solute clearance. A "high or rapid transporter" will rapidly achieve equilibration of small solutes but quickly absorb glucose from the dialysate and therefore lose their osmotic gradient and achieve poorer ultrafiltration; they benefit from shorter

dwell times to maximise fluid removal. Traditionally rapid transporters have poorer outcomes on CAPD than slow transporters but have been shown to have equal outcomes on APD (7-11). “Slow transporters” equilibrate small solutes, absorb glucose more slowly, and achieve better ultrafiltration so longer dwell times are preferable; CAPD or APD with or without day-time exchanges may be the best options.

PD fluids have changed over the years. In the 1920s first PD fluids consisted of isotonic saline, and later glucose was added. They have been largely glucose-based which are associated with negative metabolic effects and concerns relating to glucose breakdown products (GDPs) causing peritoneal damage and potentially systemic absorption increasing cardiovascular disease risk (12-14) Conventional fluids had a pH lower than the peritoneal cavity but more fluids which have a physiological pH have been developed. To minimise glucose and GDP exposure, PD fluids employing synthetic polymers and solutions with added amino acids have been introduced. These more “biocompatible” fluids are an attempt to minimise peritoneal damage and potentially prolong technique survival although further study results are awaited (15).

Despite these improvements in PD technique, and an increase in PD utilisation in developing countries, there has been ongoing decline in PD in the Western world. This is discussed in the introduction to Chapter 3.

1.2 Complications of Peritoneal Dialysis

There are various complications of peritoneal dialysis:

1.2.1 Infection

Peritonitis, PD catheter exit site and/or tunnel infection are the most frequently encountered complications; these remain the major causes of morbidity and hospitalisation for PD patients. Peritonitis may be caused by touch or trans-catheter contamination (generally caused by skin bacteria such as coagulase negative staphylococci), trans-visceral (such as gut diverticular disease causing gram negative infection) or rarely haematogenous spread of organisms. Treatment is with intra-peritoneal antibiotics according to Guidelines (16), and catheter removal if the peritonitis is not resolving. Peritonitis caused by *staphylococcus aureus* may develop spontaneously or after exit site or PD catheter tunnel infection and may be particularly severe. Fungal peritonitis is associated with poor outcome and requires PD catheter removal.

PD-related peritonitis rates vary across the world, but the reasons for this are unclear (17-23). Whether the lower peritonitis rates achieved in other countries are achievable in the UK in unselected populations, is an area of interest. Given that peritonitis is the major cause of PD technique failure in Scotland and other Western Countries, identifying risk factors or potential strategies to improve peritonitis rates could reduce the morbidity burden and potentially prolong PD technique success. Peritonitis and potential risk factors for peritonitis are discussed in Chapters 4 and 5.

1.2.2 Inadequate Dialysis and Ultrafiltration Failure

It is recognised that PD treatment duration is limited by peritoneal membrane changes over time which result in inadequate small solute clearance and/or ultrafiltration failure. Peritoneal dialysis adequacy may be expressed as Kt/V or as total creatinine clearance (litres/week/1.73 m^2), with current targets and evidence base discussed in Chapter 6. Total

creatinine clearance includes both the peritoneal clearance (i.e. the clearance achieved by the PD prescription) and the renal clearance (i.e. the residual renal function). The PD prescription may be modified to increase small solute clearance or fluid removal by increasing the number of exchanges, increasing the volume of exchanges, altering the dwell times on APD, and by using alternative dialysate (e.g. hypertonic dextrose or Icodextrin) as appropriate. Loss of residual renal function (RRF) may be a major determinant of ongoing PD adequacy, and preserving patients' RRF is an important aspect of PD treatment. RRF clearly relates to PD technique and patient survival (9, 24).

1.2.3 Complications Relating to Intra-abdominal Pressure

Rarely patients may experience problems relating to the increased intra-abdominal pressure associated with having an abdomen filled with PD fluid. Fluid leaks into the pleural cavity, peri-catheter (more likely soon after catheter insertion) or via the inguinal region into the scrotum in men. Many fluid leaks may resolve spontaneously by resting the peritoneum or reducing the dwell volumes for a period of weeks. Pleural leaks may be amenable to pleurodesis and scrotal leaks to surgical repair of any defect. Patients on PD may also develop abdominal wall herniae; umbilical and inguinal being the most common but incisional and catheter exit site herniae also occur (25). These complications are more likely in overweight patients (26). Surgical (mesh) repair of defects can be performed in order to continue PD. Given the rarity of these complications, they have not been specifically studied for this thesis but are referred to in Chapter 10 with respect to causes of PD technique failure.

1.2.4 Encapsulating Peritoneal Sclerosis (EPS)

Encapsulating peritoneal sclerosis (EPS) is a devastating complication of PD (27). EPS is thought to result from chronic intra-abdominal inflammation which is multi-factorial in origin. Prolonged PD (e.g. >5 years) represents the most consistent "risk factor" identified to date but EPS may occur after shorter PD exposure (28-32). EPS is uncommon but the exact incidence is unknown, and varies widely between studies (28-33). It is apparent from published studies that the method of calculating incidence varies such that it is inaccurate and prevents valid comparisons between studies. EPS is associated with a high mortality of up to 50% at a year post diagnosis and there is little evidence to guide best management. With no screening tests to identify those at risk or in the early stages of this condition, many clinicians are concerned about the safety of PD in general and there has been a move toward avoiding prolonged PD exposure. In Scotland nephrologists have raised concerns about the safety of offering PD to patients *at all* but no assessment of the EPS incidence or outcome had been made in our population.

1.3 Patient Outcomes on PD

Patient survival, PD technique survival and the outcomes of patients vary worldwide, and have not been specifically studied in Scotland. Comparison studies examining patient outcomes on PD versus HD have often been confounded by differences in the patient cohorts; for example PD patients as a group have traditionally been fitter by virtue of needing to perform the technique themselves at home. Initial survival studies suggested HD may offer survival advantage over PD (34) but more recent studies dispute this (35-42). It is difficult to compare HD and PD, but even within the PD population it is recognised that some patients may experience poorer survival.

Patients may stop PD because they receive a transplant, they experience technique failure or die. It is not known what predicts PD longevity in our population, but it may be helpful to be able to predict those at risk of poor outcome. If we were able to identify those who fare badly or who are most at risk of technique failure it may be possible to intervene and improve outcomes by targeting such patients with, for example, peritonitis-prevention strategies or even simply to allow timely planning of vascular access and transfer to HD.

Whether there are *modifiable* risk factors for patient or technique survival is not clear. Chapters 9 and 10 discuss patient survival and outcomes in detail.

1.4 Scottish Renal Registry

The Scottish Renal Registry (SRR) was created in 1991 by the Scottish Renal Association (SRA) as a computer based registry to collect data on every patient on renal replacement therapy (RRT) for end-stage renal disease (ESRD) in Scotland. Before 1991, Scottish nephrologists gathered data which was reported to the European Renal Association-European Dialysis Transplant Association (ERA-EDTA) as far back as 1960. When the SRR was created much of this earlier data was “back-filled” into the SRR database. All adult and the single paediatric units report data 6 monthly to the registry as computerised transfers, the Peritoneal Dialysis Audit and SRR staff work hard to ensure near 100% completeness of data. The data available are described in the overall Methods section.

1.5 Peritoneal Dialysis Literature

PD is used worldwide, but the PD population in each unit may be small, and the practice in different countries can vary. Patient demographics may also differ, such as the smaller body habitus of North East Asian patients compared to Western Europeans. With this in mind, much of the literature on PD is open to scrutiny, and uncertainty as to whether

outcomes of one study will be applicable to our own practice. National Registry data is a source of invaluable information but what it provides in scale and longitudinal follow-up, it may lack in detail. The inconsistency in PD (and indeed RRT) literature may relate to the differences in study populations, study design or inadequate patient numbers. For this reason it is desirable to conduct studies in the population for whom the results are applicable.

The completeness of the prospectively gathered SRR data for all patients treated with PD in Scotland combined with the fact that there is relatively little migration outwith the country, and it is easy to maintain patient follow-up when they move within Scotland, makes it an ideal location for population-based PD studies.

1.6 Hypothesis

The hypothesis of this thesis is that clinical practice should change to limit who is offered PD and limit how long PD is continued to minimise the risk of complications, particularly EPS, and to optimise patient outcomes.

1.7 Aims of This Thesis

The aims of this thesis are as follows:

- To establish current trends in PD utilisation in Scotland since 1999.
- To determine the rate, causative organisms, outcomes and potentially modifiable risk factors for PD peritonitis in Scotland 2000-2008.
- To determine whether measurement of renal clearance alone was sufficient to confirm adequacy targets are being achieved without concomitant peritoneal adequacy measurement.
- To quantify the incidence and cumulative risk of EPS in Scotland and characterise the EPS cases to identify potential risk factors in our population.
- To analyse patient survival and potential modifiable risk factors for reduced survival on PD.
- To identify predictors of patient outcome and technique failure in Scotland.
- To use the above analyses to establish the likelihood of continuing PD, the likelihood of suffering complications or technique failure, and the likelihood of EPS to determine who should be offered PD and how long it should be continue.

Chapter 2

Methods

2. Methods

This chapter describes the source of the data and methods that are common to all chapters. All chapters do not necessarily include the same PD cohort; for example chapter 3 includes data from all prevalent and incident patients experiencing peritonitis, whereas chapter 4 refers only to incident patients to allow valid comparisons to be made during statistical analysis. To avoid confusion the individual chapters therefore contain a brief methods section with more detail relating to the PD cohort characteristics and statistical analysis specific to that chapter.

2.1 Patient Data

The data used for this MD was the Scottish Renal Registry, the Scottish Peritoneal Dialysis Audit and separate data gathering for potential EPS cases.

2.1.1 Scottish Renal Registry Data

The Scottish Renal Registry (SRR) collects data from all patients on renal replacement therapy in Scotland. Until 2011, there were 10 adult and 1 paediatric renal unit in Scotland, all of whom contributed data to the SRR. In 2011 the two Glasgow renal units merged leaving 9 adult units in Scotland. The units are coded as shown in Appendix 1.

The units are required to report their data twice yearly with census dates on the 31st December and 30th June each year. This data is used to compile accurate dialysis histories for every RRT patient in Scotland as well as collect demographic details, laboratory results, co-morbidity information and mortality data. Much of this is now achieved through computer connections, with a great deal of support from the SRR staff. The SRR has prided itself on the completeness of the dataset, and much of this is the result of the hard work and dedication of the SRR staff. After each census date there follows a period of

months during which the SRR staff contact the units to chase up the data, fill any gaps and clarify inconsistencies. There are also automated checks within the system to identify gaps and incorrect data (such as urea reduction ratios being reported on a patient supposedly still on PD). Over the years various projects have involved linkage with other Scottish registries (cancer registry, diabetes registry) which further increases the scope of the dataset.

2.1.2 The Scottish Peritoneal Dialysis Audit

The Scottish PD Audit was started in 1999. It consists of a paper questionnaire which PD nursing staff complete every 6 months for every patient on PD in each of the adult PD units. This prospectively gathered data includes:

- PD population at the start and the end of the 6 month period
- Proportion of the PD population on APD and CAPD
- Total number of treatment months for the PD population in the 6 month period
- Number of patients starting and stopping PD
- Source of patients starting PD (new to RRT, from HD, failed transplant, moved house)
- Reason for stopping PD (transplant, death, technique failure)
- Cause of technique failure
- Details of all peritonitis episodes (white cell count (WCC), organism, time to resolution, outcome (cure, refractory, relapse, recurrence, death, technique failure))
- Adequacy test results (renal clearance, peritoneal clearance, total clearance, BMI)
- Basic laboratory results

The SRR staff have ensured 100% returns of the audit forms over the years and optimised accuracy by routinely checking the patient numbers tally with previous returns and contacting units when there are inconsistencies.

The PD audit data were handwritten but did not include a unique identifying number for patients. Instead the patients were identified by name or, unfortunately, by initials in a large proportion of cases. This introduced an added complication and considerable extra work to ensure the patients were identified correctly and matched to their SRR unique identifier number to allow us to link audit data to the registry database. Gaps were filled by contacting the units and, if required, travelling then units to check computerised records. With hindsight, asking the units to identify patients by their SRR number would have added little to their workload, but saved a huge amount of effort for this thesis.

2.1.3 EPS Study

For the EPS study we asked units to identify potential cases diagnosed from 1st January 2000 onwards. Initially we collected all cases from the incident and prevalent PD population 1st January 2000- 31st December 2007 but thereafter just collected details of patients from the 1238 incident PD cohort identified from an SRR search in early 2008. This allowed an accurate calculation of incidence. Units were contacted at intervals (2006, 2008, mid 2009, mid 2011) to identify further cases diagnosed since the last data collection. On each occasion I travelled to the units to examined patients' casenotes, radiology results, pathology results and any electronic patient databases to determine whether cases met the ISPD 2000 criteria for EPS diagnosis (43). Cases were excluded if there was an alternative explanation for the clinical presentation including TB, liver disease, intestinal perforation or alternative surgical cause for adhesions. The data gathered for EPS cases are listed in the Dataset section below.

2.2 Study Population

We focussed our analysis on patients on PD during the time period after 2000 for several reasons:

- PD technique improved in the 1990s, but has remained almost unchanged since 2000 in Scotland therefore technique changes should not confound our results;
- The PD audit began in 1999 providing detailed, prospectively gathered data after this date; and
- This time would include sufficient numbers of patients and follow-up for meaningful analysis, but still reflected current practice.

The PD audit gathers data on all incident and prevalent patients since 1999, but as prevalent patients may have commenced PD many years prior to 1999 it would be invalid to compare outcomes between what may be a very heterogeneous population. However, data relating to general trends in PD (Chapter 3), peritonitis rates (Chapter 4) and the analysis relating to PD adequacy (Chapter 6) have used both incident and prevalent patients as stated in these Chapters' Methods sections. Other chapters have focussed primarily on incident patients to allow comparisons between groups, and accurate incidence calculations.

2.2.1 The Prevalent PD cohort

For chapters 3, 4 and 6 the data described are from the prevalent PD population during the time period specified and were obtained from PD audit and SRR data.

2.2.2 The Incident PD cohort

For the purposes of comparisons between groups, we only used data from incident patients over 18 years old starting PD between 1st January 2000 and 31st December 2007. We included all patients even if that exposure was under 3 months.

Early in 2008 we ran the first search of the SRR database to identify all patients exposed to PD for the first time between 1st January 2000 and 31st December 2007.We identified **1238** patients and this cohort we intended to follow-up when establishing the EPS incidence.

Since 2008 and beyond there has been a huge effort to check SRR data, particularly for inaccurate coding. During this process it was recognised that some patients had incorrectly been coded as intermittent PD (which is an obsolete code and should not have been used). These patients were missed from the first dataset. When updating the dataset in 2009 to carry out further analysis, we identified further patients who had commenced PD toward the end of 2007 but had not yet been reported to the SRR and were therefore also missed from our first search. This meant that the truly accurate incident PD population comprised **1324** patients, and not 1238 as first identified. Of note, the vast majority of the 86 patients had had <1 year of PD, and many had had <1 month. A decision was made that for the purposes of the EPS incidence study we would continue to follow the cohort of 1238 patients. For all other analyses we would use the complete cohort of 1324 patients.

This highlights a problem of registry data; namely the inherent delay in updating the database. Although we are confident that the data is accurate, we recognise that there will be a delay and therefore decided to end our follow-up on 30th June 2011, but not download the final dataset until February 2012.

2.2.2.1 PD Exposure

Patients may have changed between dialysis modalities during the study period. Please note that the PD exposure time for each patient refers to their *cumulative* exposure during the study period, but that exposure may have been achieved during several separate PD treatment episodes rather than one continuous episode.

2.2.3 The Dataset

The audit data were combined with downloaded SRR data to create the following databases:

- **Peritonitis Database**: Details of all peritonitis episodes, organisms cultured and outcome for all incident and prevalent patients 2000-2007 identified by individual patient and also combined by unit.
- **Adequacy Database:** Details of all adequacy test results for incident and prevalent patients 1999-2007
    - Included renal clearance, peritoneal clearance and total corrected clearance.
- **Incident Patient Database:** Included the following data by combining registry data and results from the above 2 databases for all incident patients starting PD between 1st January 2000-31st December 2007:
    - Patient demographics (age, gender, race)
    - PD Unit
    - Deprivation category (Scottish Index of Multiple Deprivation Score 2006)*
    - Cause of primary renal disease
    - Whether patient was diabetic or not (even if not the PRD)
    - Body mass index at start of PD (within 6 weeks prior to starting PD)
    - Serum albumin at the start of PD (within 6 weeks prior to starting PD)
    - Adequacy measurements/residual renal function measurements
    - Full RRT history
    - Date of first RRT and first PD
    - PD exposure to several census dates depending upon analysis
    - Date of death
    - Details of all peritonitis episodes 2000-2007 by patient
    - Outcome of PD (death, transplant, technique failure)
    - Cause of technique failure (where relevant)

- **Encapsulating Peritoneal Sclerosis (EPS) Database:** included the above data for all cases of EPS diagnosed 2000-2011 as well as the following:
    - Clinical features at presentation
    - Date of diagnosis
    - Imaging results
    - Surgical findings at laparotomy/laparoscopy
    - Specific treatment commenced
    - Outcome/survival
    - Exposure to hypertonic dextrose (3.86% or equivalent)
    - Exposure to extraneal
    - Details of exposure to betablocker drugs, MRI, ACE inhibitor/ARB drugs

• * The Scottish Index of Multiple Deprivation (SIMD) 2006 score is a measure of deprivation incorporating 37 factors in seven categories (current income, employment, health, education, geographic access to services, housing and crime). It is ranked from 1 (least deprived) to 5 (most deprived). It is updated every 3 years and an area's ranking is relative to other areas; for example the rank may improve despite there not having been a real improvement in the factors contributing to deprivation in the area. For this reason it is important to use the score relevant to the time period being studied; in this case the 2006 was most appropriate as it is based upon data after 2003.

2.2.4 Follow-up

All incident patients have been followed up for a minimum of 3.5 years from the 31st December 2007 until the study end on 30th June 2011.

2.2.5 Statistical Analysis

Statistical analysis was carried out using SPSS version 19. Specific analyses performed are described in the individual chapters. P values of < 0.05 are generally taken as statistically significant but it is acknowledged that when making multiple comparisons it would be appropriate to lower the significance level, accepting lower p values as significant.

2.2.6 Ethics

Advice was sought from the West of Scotland Research Ethics service who confirmed no further ethics application was required as the work would be covered by Ethics under the auspices of the SRR and National Audit.

2.2.7 Limitations

Registry data has inherent limitations namely missing data, potentially fewer clinical details, and a lag time to updating patient details. The relatively small size of Scotland, and close working relationship between registry staff and the PD nurses and doctors from each unit has meant that potential inaccuracies or incomplete audit data are recognised and dealt with in a timely fashion. By allowing an 8 month period to elapse before downloading relevant patient details from the SRR database we have minimised the likelihood of incomplete or inaccurate data. Being a retrospective analysis, this thesis is limited by the data that were available; the dataset does not include details of the patients' dialysis prescriptions, brand of dialysate used, peritoneal equilibration test results, detailed comorbidity or functional status. In addition, specific aspects of the PD technique such as exit site prophylaxis, exit site dressing and details of patient training/re-training methods are not available retrospectively. We had details of reported adequacy tests for patients but without knowing the PD prescription details and any modification to this prescription we felt it would be difficult to draw any meaningful conclusions with respect to change in adequacy results and patient outcomes. We did not have details of the cause of death

Chapter 3

Trends in the Peritoneal Dialysis Population in Scotland in the post-Millennium

3. Trends in Peritoneal Dialysis Population in the Post Millennium

3.1 Renal Replacement Therapy

Provision of renal replacement therapy (RRT) has changed over the past 5 decades from a time where a select few young, non-diabetic patients were dialysed. In the early 1960s only 17% of those on dialysis were over 44 years old, compared to 82% at the beginning of the millennium (44). The proportion of patients with diabetes mellitus (DM) as their primary renal diagnosis (PRD) has increased from a time when none were offered RRT in the 1960s, to around 20% by 2000. The RRT population continues to grow worldwide; in Scotland there were 106 patients on RRT in 1970, and 3244 by the millennium (45-47).

Transplantation is the treatment of choice, and means of expanding the donor pool have been a major focus for nephrologists. Living donation is now routine when a suitable donor is available, and options for paired or a chain of paired transplants are now available. Haemodialysis (HD) remains the most prevalent form of dialysis for adult patients, and we have seen recent advances in the form of home haemodialysis, high flux dialysers and improved, sometimes heroic, vascular access techniques.

Home dialysis, that is HD or peritoneal dialysis (PD), is relatively underutilised in the UK compared to other countries (45). The number of home HD patients in Scotland has fallen steadily from 79 in 1995 to 56 by 1999 despite increasing numbers of patients commencing dialysis (44). The proportion on PD until the start of the millennium was 20-30%, varying by unit. PD gives patients the opportunity to dialyse at home, and offers more freedom to travel.

However, the proportion of patients using PD varies considerably between units, countries and continents. Some of this variation relates to availability of alternative home therapies (home haemodialysis), satellite dialysis units, rates of renal transplantation and, in some countries, healthcare provision and financial considerations.

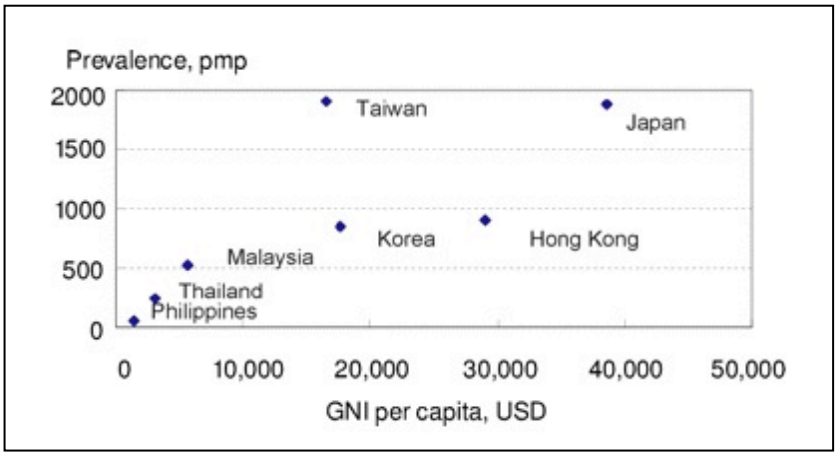
Trends in PD Worldwide

There were 196,000 PD patients worldwide in 2008, accounting for 11% of all RRT patients (48). Of note the majority (59%) were treated in developing countries which have seen an increase of 24.5 patients per million population in the 12 years 1997-2008 (48). Over the same time period there was an increase in the absolute PD population in developed countries of 21.8 patients per million population but the proportion of RRT patients treated with PD has fallen by 5.3% in developed countries. Therefore the increase in PD numbers reflects an overall increase in the population requiring dialysis rather than the proportion being maintained on PD (48).

Worldwide the proportion of patients maintained on PD varies dramatically. In Japan, PD prevalence peaked at 5.3 % of RRT patients, and has been closer to 3.6% in recent years (49). In China approximately 9.5% of RRT patients are on PD, in India 21% use PD whilst in Hong Kong up to 80% of prevalent patients use PD (50, 51). The situation in Hong Kong is a result of a “PD First” policy started during a time of limited HD capacity and lower cost of PD over HD (51). In some health care systems the choice of RRT is heavily influenced by the relative cost of PD versus HD. In India a PD regime with 3 daily exchanges costs as much as twice weekly HD, and a regime with 4 exchanges is more expensive than HD (50). Indeed, the prevalence of dialysis has been shown to correlate closely with the economic state of countries (figure 1).

Choice of RRT modality in some countries will not purely be the result of patient and clinician preferences, but rather reflects the relative affordability of one type of dialysis over another. This makes comparisons between countries and healthcare systems difficult.

Figure 1. Prevalence of dialysis per million population in North East Asian countries (from reference (51))



Other North East Asian Countries followed Hong Kong's lead, offering free PD for end stage renal failure (ESRF) when previously the only option was paying for HD (Thailand) and increasing the reimbursement paid by the government for dialysis provision such that PD would draw in far more money to each dialysis centre (Taiwan). Both these countries have since seen a massive increase in PD population in a very short space of time (51).

Another factor driving PD expansion in North East Asian countries is the enthusiasm of the nephrologists who hold regular training courses and have been key to the overhaul of RRT provision in these countries (50, 51).

Surveys of nephrologists in the UK, Canada and the USA at the start of the millennium report that around 35% of patients should be maintained on PD (52-54). Despite this, Western countries have almost universally seen a reduction in PD usage. In Scotland, PD use peaked in the 1990s with around 22% of prevalent RRT patients on PD, but in 2000 this had already fallen to around 14% (47).

Possible Reasons for falling PD Prevalence in Developed Countries

There are several possible reasons for this: ageing RRT population, increased availability of hospital-based HD, earlier outcome studies suggesting HD offered a survival advantage, concerns about EPS and adequacy of PD, less exposure to PD and reduced experience for nephrology trainees. The cheaper cost should make PD more financially attractive in North America but should be unlikely to influence choice in the UK with the national Health Service (NHS) theoretically providing unlimited access to whoever chooses PD (55). There has been a shift in opinion to avoiding prolonged PD, e.g. >5 years therapy, because of the increased risk of EPS and inadequate dialysis/ultrafiltration associated with longer time on PD. Whether this has translated to a fall in prevalent PD numbers is not clear.

Changes in RRT and PD Population Demographics

The RRT population is ageing worldwide. Frequently elderly patients opt for HD over PD. This may be due to physical infirmness, poor vision, cognitive impairment and lack of help at home. However, there is growing interest in the PD literature for the role of PD in the elderly, with a move toward minimising time spent in hospital for patients in general (56-58). The option of *Assisted PD*, which has been standard practice in France for many years, is a recent addition to the UK, but is not yet in widespread use. In France PD is predominantly a treatment of the elderly with 50-60% of patients being >70 years old (59, 60).

In Scotland PD usage has decreased as shown in the Scottish Renal Registry (SRR) overall RRT prevalence figures in the past decade. The SRR report does not tell us if this decrease is mainly attributable to a reduction in the *prevalent* PD population, e.g. resulting from a reduction in the numbers of patients with prolonged PD exposure (>5 years), or changes in

the *incident* PD population. Are certain units more likely to initiate PD? Has there been a change in the demographics of the incident and prevalent PD patients?

3.2 Study Aim

The aim of this study was to use the PD audit data and SRR database to look for changes in the incident and prevalent PD population between 2000-2011 at unit and national level.

3.3 Methods

The Scottish Renal Registry collects data for all patients on renal replacement therapy. This study uses data from all 10 adult renal units in Scotland from the years 1999-2011 to calculate the incidence and prevalence of RRT patients. Data relating to the prevalent PD population have been obtained by searching the SRR database for the census date 30th June 1999 for each year to 2011. The data include patient demographics (age, gender), unit, duration of PD on census date, previous history of transplant or HD.

Analysis of the incident PD population relate to the period 1st January 2000-31st December 2007 for whom we have detailed clinical data obtained from the SRR database and the national PD audit. The National PD Audit is a questionnaire completed 6-monthly by PD staff in each of the 10 adult renal units in Scotland. It includes details of all patients starting and stopping PD, proportion on APD, peritonitis details, causes of technique failure, adequacy test results, patient height/weight, as well as haematology and biochemistry blood results for each patient. Data relating to patients' primary renal diagnoses (PRD), diabetic status, postcode (from which deprivation category was calculated using Scottish Index of Multiple Deprivation score "SIMD 2006"), dialysis history, date of death and unit were downloaded from the SRR database.

Data are described as mean and standard deviation, median and interquartile range. Comparisons of categorical data were made using Chi-square test for proportions, and comparison of means for continuous data using ANOVA. Later chapters describe peritonitis, technique failure and patient outcomes in PD patients in detail and trends relating to these are not repeated here.

3.4 Results

3.4.1 RRT in Scotland 1999-2011

Incident Population

The annual incidence of new patients starting RRT in Scotland has been fairly stable at 110 per million population (PMP) in 1999, to 97 PMP in June 2011 (SRR Report). The median age of patients starting RRT has been constant at 63-65 years 1999-2011; approximately 25% of patients are >75 years old, 25% aged 65-74 years, 30% aged 45-64 years, 17% aged 20-44 years and 3% <20 years old.

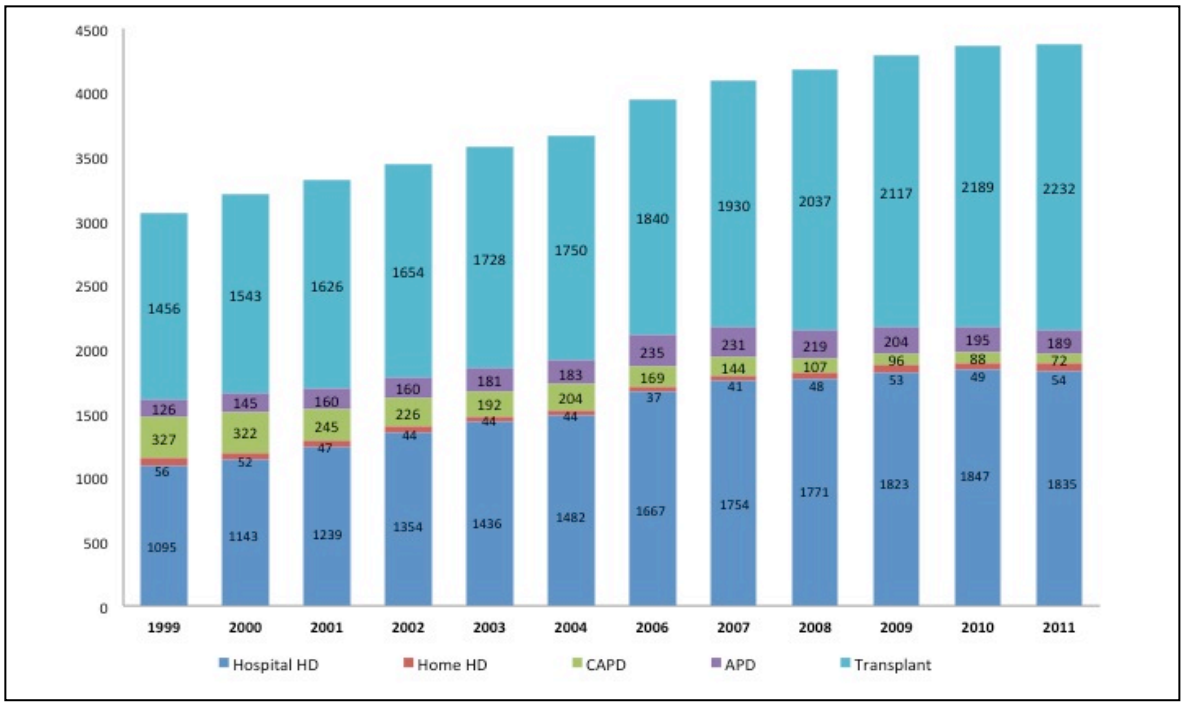
The proportion of patients starting HD as the mode of first RRT has increased from 74.0% in 1999 to 80.6% in 2011, with a corresponding fall in the proportion starting PD from 24.8% to 17.1% in the same time period. The proportion of incident patients who received a pre-emptive transplant increased from 1.2% in 1999 to 2.4% in 2011.

Prevalent RRT Population

The prevalent RRT population has grown over the study period from 3060 patients to 4382 patients. The proportion on HD has increased from 35.8% in 1999 to 41.9% in 2011. The numbers of home HD patients remain small with a prevalence 0.9-1.2% during the study period. The proportion maintained on PD has fallen from 14.8% to 5.9%. There has been a

slight increase in the proportion with transplants; rising from 47.6 to 50.9% between 1999 and 2011.

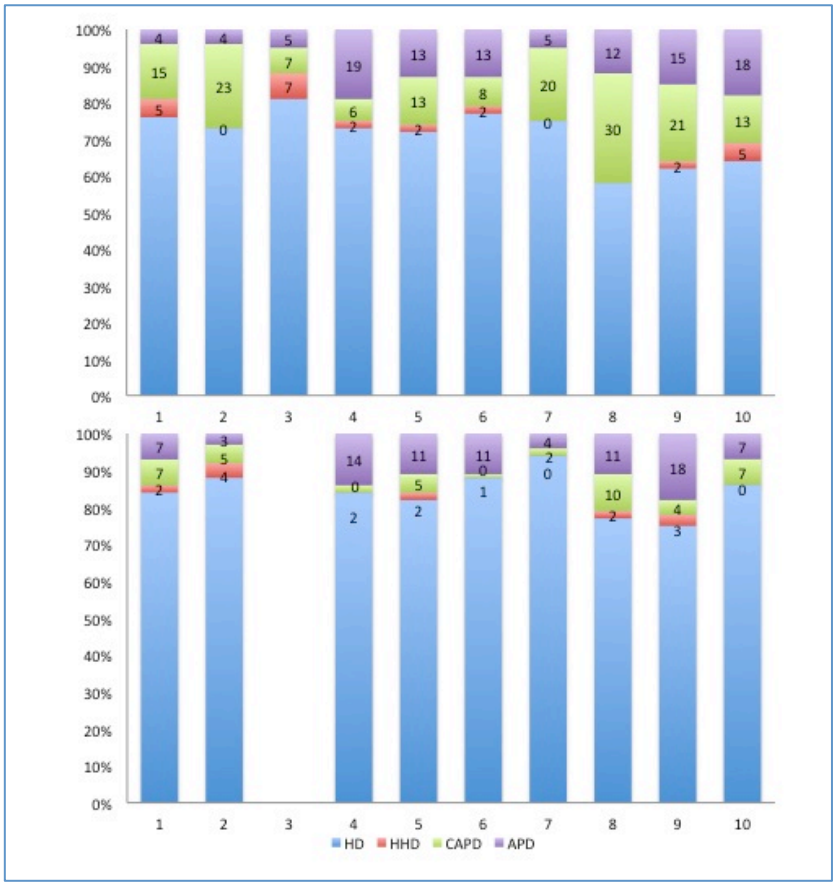
Figure 2.The prevalent RRT population (absolute numbers of patients) showing proportion on each modality.



Prevalent RRT Patients by Unit

Comparing 1999 to 2011, the most obvious change is an overall increase in proportion of patients on hospital HD in all units and the marked decrease in PD. Units 8 and 9 still have >21% of patients on PD compared to <16% in every other unit. Unit 8 covers a predominantly rural location, including the Western Isles, Shetland and Orkney.

Figure 3. Proportion of prevalent RRT patients (excluding transplanted patients) comparing 1999 (upper graph) and 2011 (lower graph) by units



Note units 2 and 3 merged in 2011 hence the absence of unit 3 on lower graph.

3.4.2 Incident PD Patients

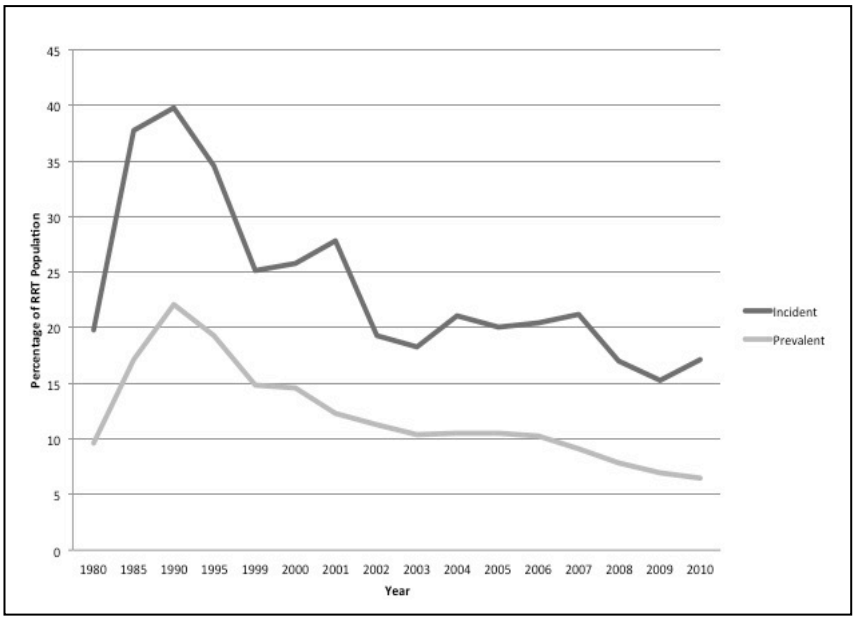
We have detailed clinical characteristics for the incident patients starting PD 1st January 2000- 31st December 2007 inclusive. Using this data there has been no change in the incident PD population in the proportion of males, mean age at starting PD, BMI at start of PD, proportion from each deprivation category, serum albumin at the start of PD, and the proportion of diabetics or spread of primary renal diagnoses (PRD) between 2000-2007.

Change in Incidence of PD over time

Following a peak incidence of 40% of incident RRT patients in 1990, the incidence has fallen steadily since, but may be levelling off at around 20% (figure 4).

The fall in the PD incidence mirrors that of PD prevalence, but the prevalence always remains 15-20% lower. This reflects PD longevity, including technique survival, which is analysed in a later chapter. It is worth noting that the gap between incidence and prevalence of PD persists; if PD survival were improving whilst PD incidence was falling one would expect the lines to converge

Figure 4. Incidence and prevalence rates for PD in Scotland 1980-2010



3.4.3 Prevalent PD Patients

PD Population and Proportion on APD and CAPD

The prevalent PD population has decreased from 436 in June 1999 to 247 patients in June 2011, representing a 43.3% fall in PD patient numbers. This is equivalent to a fall from 86 to 47 PD patients per million population. Some units have seen an almost 80% fall in their PD patient population, and only 2 units have maintained the same number of prevalent patients (table 1).

Table 1.PD population by audit period and unit showing the change over time.

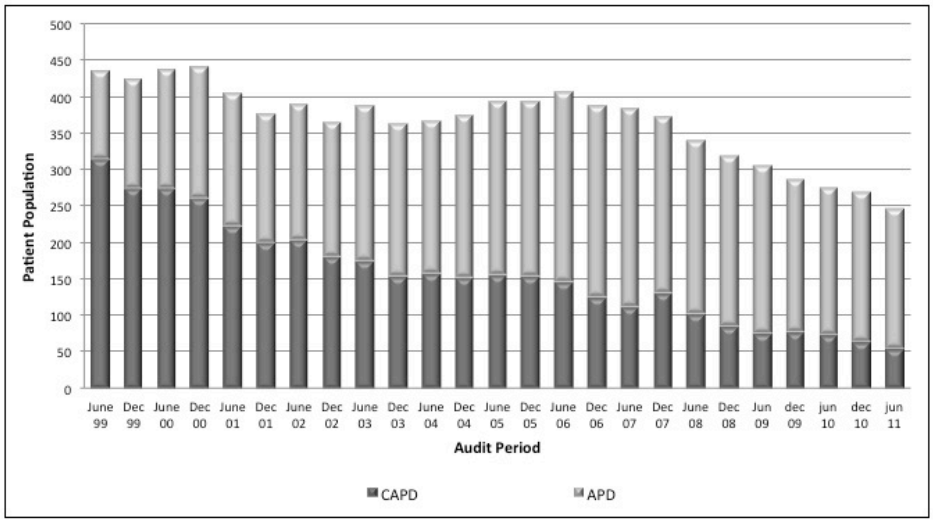
Unit	Audit Period													
	June 99	Jun 00	June 01	June 02	June 03	Jun 04	June 05	June 06	June 07	June 08	June 09	June 10	June 11	% change
1	32	36	26	28	33	33	44	35	33	36	32	32	22	- 31.3
2	97	87	73	80	78	77	73	69	58	46	46	38	52	- 46.4
3*	78	65	45	39	40	32	30	26	29	24	18	16	-	- 79.5
4	18	24	29	22	21	15	22	30	30	26	28	25	26	+ 44.4
5	53	62	57	50	45	49	55	67	74	74	64	57	47	- 11.3
6	41	36	39	31	26	33	50	47	43	30	27	22	24	- 41.5
7	33	38	37	39	33	32	36	28	21	15	13	14	7	- 78.8
8	31	31	30	40	31	36	30	44	41	33	24	22	18	- 41.9
9	40	45	43	40	49	42	39	45	41	41	39	38	41	+ 2.5
10	13	13	26	21	31	17	15	15	13	16	15	11	10	- 23.1
All Units	436	437	405	390	387	366	394	406	383	341	306	275	247	- 43.4

* Note unit 3 merged with unit 2 in 2011. The % change in PD numbers for this unit based on difference between 1999 and 2010 figures.

Proportion of Patients treated with CAPD and APD

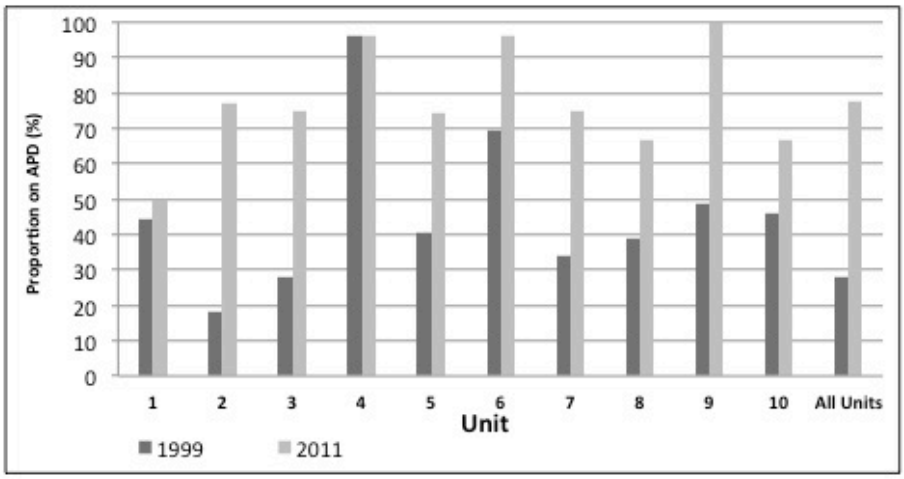
The proportion of patients being treated with APD has increased steadily over the 12 years 1999-2001 from 28.0 to 77.7%, shown in figure 5.

Figure 5. PD population and proportion on APD and CAPD 1999-2011



Some units have embraced APD from the start, with the majority of patients on this modality in 1999. Other units had a minority using APD but now all units maintain over 65% of their patients on APD. The change in proportion on APD comparing 1999 and 2011 is shown in figure 6.

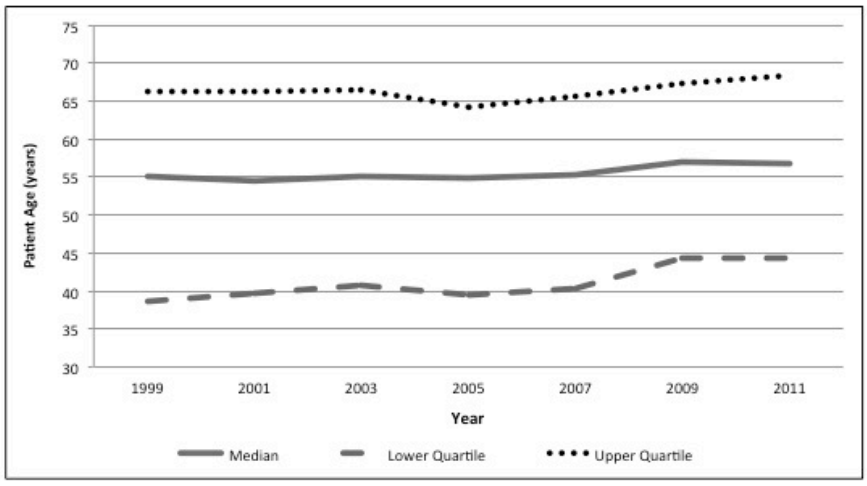
Figure 6. Proportion of patients on APD by unit comparing June 1999 and June 2011



Patient Demographics

The mean age of the prevalent population has increased from 53.9 (SD 17.6) to 57.3 (SD 18.0) years between 1999 and 2011 (p=0.01). The mean age at the start of PD has also increased from 51.4 (SD18.0) to 54.6 (SD18.3) years in the same time period (p=0.03). The proportion of males has not changed at around 57% throughout the period.

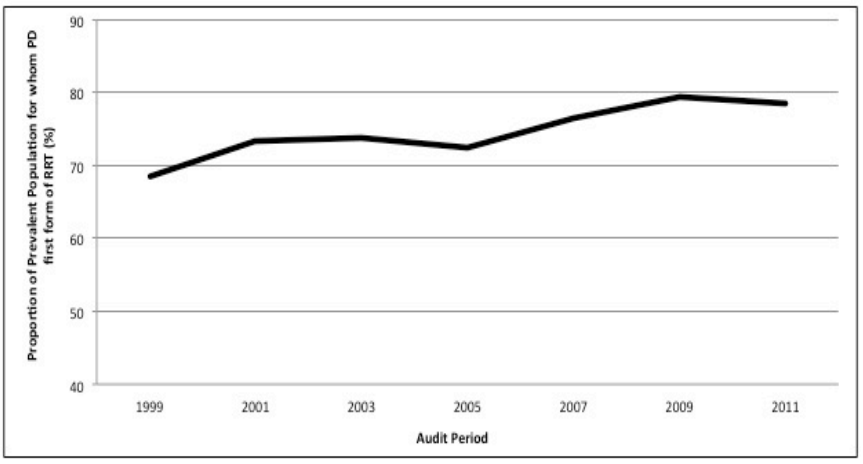
Figure 7. Median patient age with upper and lower quartiles 1999-2011



Stock and Flow

The "source" of patients starting PD has remainded fairly stable with 60-70% new patients starting RRT for the first time, 25-30% from HD and 8-10% following a failed transplant. Examining the proportion of prevalent patients for whom PD is their first form of RRT, there has been an increase from 68.5% in 1999 to 78.5% in 2011 (p=0.004) (figure 8).

Figure 8.Proportion of Prevalent PD population for whom PD is their first form of RRT 1999-2011.



PD Exposure

The mean PD exposure has not changed significantly over the 12 year period 1999-2000 but if anything is showing a trend toward increasing; 799 days (SD 819) in 1999 to 828 days (SD 770) in 2011 (p=ns).

When split into PD exposure groups there is a significant difference in the proportion on PD for a given time period (p=0.03). Somewhat surprisingly the proportion of prevalent PD patients who have been on PD for >5 years is almost the same in 2011 (9.2%) as it was in 1999 (10.1%) (table 2). However, the number of patients has decreased significantly overall so the proportions will be more liable to statistical bias in more recent years. It may be that if patients have managed to reach 5 years of PD then they are not transplant candidates (or would have had a transplant by then) or represent a group of patients for whom the social benefits of the therapy outweigh the risks.

Given the general feeling worldwide that at 5 years of PD we should be thinking about transferring a patient to another modality because of the risk of EPS, one might have expected to see a fall in the proportion of patients on PD for >5 years but this is not the case.

Table 2. Number and percentage of prevalent patients on PD for given duration of time according to year of audit.

PD Exposure (Yrs)	Number of Patients (%)				
	1999	2003	2007	2011	Total
≤ 1	172 (37.6)	138 (34.8)	120 (30.8)	86 (33.1)	516 (34.3)
> 1-2	99 (21.7)	87 (22.0)	107 (27.4)	59 (22.7)	352 (23.4)
> 2-3	70 (15.3)	64 (16.2)	77 (19.7)	45 (17.3)	256 (17.0)
> 3-4	47 (15.3)	60 (15.2)	32 (8.2)	29 (11.2)	168 (11.2)
> 4-5	23 (5.0)	20 (5.1)	30 (7.7)	17 (6.5)	90 (6.0)
> 5	46 (10.1)	27 (6.8)	24 (6.2)	24 (9.2)	121 (8.1)
Total	457	396	390	260	1503

3.5 Discussion

The SRR National PD audit provides comprehensive data allowing accurate analysis of national trends and helping overcome the bias of single unit studies with small PD populations. Such data is valuable at a local level, to allow units to review their practices, but also at a national level to help service planning; fewer patients using PD means more patients requiring alternative renal replacement therapies. Our data have shown a progressive decline in the Scottish PD population, with an increasing proportion on APD and a progressively older PD population. In the absence of any clear evidence that PD offers inferior outcomes or survival compared to HD, the reason(s) why PD prevalence is falling is important to examine. In Scotland there are no financial incentives, which eliminates this potential source of clinician bias when deciding modality of RRT. If the trend represents changing clinician attitudes influencing patient choice, then is this judgement justified by current evidence?

3.5.1 A Falling PD Population, but Rising APD

The prevalent PD population in Scotland continues to progressively decrease (from 87 to 76 per million population, an 8.7% pmp fall) or a fall from 14.8 to 5.9% of the prevalent RRT population. Similar declines have been seen in Australia (24 to 10.6%) and New Zealand (55 to 21.8%) in the same time period. The UK Renal Registry data demonstrates a 7.8% fall in PD prevalence 2008-2009 (and a fall of 5.1% pmp 2005-2009) (45, 61).

With the advent of APD, which may offer better quality of life by avoiding daytime exchanges, one might have expected an increase in PD usage in general but this has not been the case. The proportion of PD patients using APD has steadily increased from 28% in 1999 to over 77.7% by mid-2011. The increasing proportion of patients receiving APD in Scotland is in keeping with international trends, but the proportion is considerably higher in Scotland with only approximately 50% of the remainder of the UK PD population on APD (61, 62). There is wide variation in the proportion of patients in each unit on APD in Scotland, with 50% in one unit and 100% in another by 2011. The same variation occurs in the rest of the UK, as well as between and within countries worldwide (45, 61, 62). The ANZDATA report (2007) shows that the proportion of PD patients who are on APD increased to 29% and 48% in New Zealand and Australia, respectively.

APD offers greater flexibility for patients to work or at least not be bound to regular daytime exchanges. APD has been associated with improved technique survival and can continue even in anuric patients which adds to its attraction over CAPD (63, 64). One might have expected that increase in APD usage would be mirrored by an increase in younger patients who would be more likely to opt for a therapy that would fit around work. This is not apparent in our population, as the population is in fact older in recent years.

However one can see that APD is also a more attractive option for elderly patients particularly if relying on carers as there are less connect/disconnect procedures.

3.5.2 Possible Explanations for the decline of PD

Increased options for HD?

It is recognised that PD uptake relates to availability and proximity to haemodialysis facilities, whereby the units with fewer HD spaces (or satellite units) that cover the widest geographical area tend to have greater PD uptake and longer duration of PD. Likewise, changes in availability of dialysis facilities in the larger dialysis units, whether temporary or permanent, may impact significantly on national prevalence data. There has been an expansion in the number of HD satellite units in Scotland, and some units are able to offer more evening or even overnight dialysis which adds to the HD capacity of the unit and provides more flexibility for the patient. These changes have been established for several years and yet the fall in the prevalent PD population persists year on year in Scotland which suggests an alternative explanation for this ongoing pattern.

Reduced duration of PD?

The proportion of incident RRT patients starting on PD has fallen to a lesser extent (24-17%) which would suggest that the fall in the prevalent population is not simply related to fewer patients starting, but also fewer patients continuing PD. The general impression in Scotland is that nephrologists are reluctant to continue PD long-term, at least in part driven by the recommendation to review ongoing PD treatment beyond 3 years, and certainly beyond 5 years because of an increasing risk of EPS (65).

However the mean PD exposure of the prevalent PD population towards the end of the study period is comparable to that in 1999, and if anything may be slightly longer. This is surprising, particularly as there appeared to be a fall in the proportions on PD >5 years in the 2003, and 2007 analysis. The population maintained on PD has fallen and it may be that there will always be a steady proportion of patients for whom PD is the only option (such as of lack of vascular access) or who wish to continue despite being counselled about the risks of EPS. We were not able to assess Scottish nephrologists' practice with respect to how many actively counsel their patients about EPS and limit PD to <5 years.

Increasing age and co-morbidity of the ESRF population and contraindications to PD?

The RRT population is getting older and therefore may carry a greater co-morbidity burden compared to previous decades, although a US study concluded that these demographic changes were insufficient to explain the fall in PD utilisation (66). Other possible causes include the attitudes of staff and patients toward PD. Patients are encouraged to choose the modality of RRT, but not all patients will be suitable for all modalities, and may therefore have restricted options. However it is widely accepted that at least two-thirds of patients will not have a contraindication to either HD or PD and could theoretically commence either (67-70). It has also been shown that the likelihood of a patient being offered PD is *not* related to the presence of medical contraindications to the therapy and in the US as few as 25% of HD patients report having had PD discussed with them (70, 71). When efforts are made to ensure informed choice, the proportion opting for home therapies increases (72, 73).

What constitutes an absolute and what constitutes a relative contraindication to PD seems to be a source of disagreement among nephrologists (74). Relative contraindications include obesity, lack of personal hygiene, physical infirmity, poor vision and lack of social

support (75). Previous abdominal surgery is now not necessarily a contraindication to PD (76). Different perceptions of PD contraindications may influence clinicians' practice.

Clinician or unit attitude toward PD?

This is difficult to measure, but undoubtedly plays a role given that some centres in Scotland have seen a fairly dramatic fall in PD numbers whilst others have remained stable or increased in size. Most renal units in the UK have formal pre-dialysis education programmes that aim to inform patients of the options available and allow them to a decide their preferred mode of renal replacement therapy. Despite this, patients will be influenced by the attitudes of staff providing education, and despite their best efforts staff may be unable to hide their preference for one RRT modality over another.

Studies have shown that if given free choice, after HD and PD education, 45-50% of patients would choose PD, but this proportion is significantly lower in elderly patients (67, 69). The NECOSAD study group showed that patients >70 years old were six times more likely to choose HD than those aged 18-40 years whilst a Canadian study showed that more elderly patients will choose PD if community assistance is available (69, 77).

PD tends to be looked after by certain members of the clinical team, whilst others have more limited input. Clinicians will be influenced by personal experience, and may be particularly swayed by negative associations such as previously fit patients succumbing to peritonitis or EPS. A US survey found that those working with PD patients were more likely to favour PD and those predominantly working with HD were swayed more toward HD (78). Surveys of US renal units suggest that current training programmes do not have enough PD patients or provide sufficient training for trainee nephrologists to develop the required expertise to feel comfortable caring for PD patients (79, 80).

Indeed the same survey of US nephrologists found that although 92% of US patients are maintained on hospital HD, only 6% of nephrologists would choose this modality for themselves, so the question of how clinician attitudes may influence their practice is clearly complicated (79). The reality is that familiarity with a treatment is likely to make it easier to counsel patients about starting that treatment. It also makes it more likely that potential difficulties or complications will have been met and overcome before and so the chances of longer term PD treatment success is therefore more likely.

The falling PD population to single figures in some Scottish renal units, means that nursing and medical staff will have limited exposure to the treatment. PD in Scotland has evolved into a nurse-led outpatient treatment which further reduces the day to day PD exposure for nephrology trainees, who may develop a skewed opinion of PD based upon the few patients who end up in hospital with peritonitis or other complications. Although the nurses are running the PD units, it is often the doctor at the nephrology clinic who provides the initial dialysis modality education. It is easy to foresee that a vicious circle may perpetuate itself whereby less experience of PD may make a clinician less comfortable about encouraging new patients to opt for the treatment. It may also mean that PD nurse staffing levels gradually decrease and the capacity of the programme falls so it is no longer an option to maintain a large proportion of patients on PD as there are not enough trained staff.

When surveyed at the start of the decade, UK nephrologists stated that in an “ideal dialysis system” 38% of patients would be dialysed on PD (subdivided into 19% APD, 16% IPD, 3% CAPD) (53). Data suggest that patients are equally likely to choose PD or HD if fully informed about both modalities (69, 81). Theoretically, patients referred early may be better informed and more likely to make adaptations to their lifestyle or have the

confidence to try to use a home dialysis therapy. Similarly, late referrals are more likely start dialysis as an emergency, and therefore more likely to undergo haemodialysis (often via temporary access) rather than PD (82). However, when early referrals (>30 days prior to RRT commencement) were compared to late referrals (<30 days prior to RRT commencement) there was no difference in the proportion eventually ending up being treated with HD and PD longterm; although more of the late referral required initial HD, many transferred to PD thereafter (83).

When North American nephrologists were surveyed in 2001, they agreed that 40% of prevalent established renal failure patients should be maintained on PD to maximise cost-effectiveness, quality of life, survival and general well-being (52, 78). At that point only around 13% of prevalent patients were on PD (84). It is interesting that the disparity between the nephrologists survey responses and observed practice have been attributed in part to the influence of financial considerations (78). Scottish nephrologists do not have this concern as the patients are treated via the NHS, and there is no financial incentive for the medical staff when determining which dialysis modality a patient receives, yet there remains a marked difference between what the nephrologists say they want and what they practice.

Clinician attitudes justified by outcome data?

It seems likely that the major determinant of the falling PD population relates to unit or clinician preference. Is this attitude justified by the outcome data comparing HD and PD? Early comparison studies suggested that there may be a survival benefit for HD (34). Subsequent studies have consistently shown that there is either no difference between modalities or a survival advantage associated with PD in the first few years of therapy, the extent or duration of which is influenced by age, diabetic status and co-morbidity (35, 36,

38, 42, 85). USRDS data 1996-2003 looking at 12 month outcomes for PD versus HD patients found that outcomes (death and technique failure) were steadily improving for PD, but were unchanged for HD (66). This was at a time of improvement in PD technique and reduction in peritonitis rates and therefore it is not known if there has been ongoing improvement. Certainly current data cannot be used as justification for *not* offering the choice of dialysis modality to patients. Add to this the evidence that PD patients report a greater satisfaction with care than HD patients, and there is another argument for increasing rather than decreasing PD usage (86).

In summary, current patient outcome data would at least favour a neutral attitude to HD versus PD, or potentially support PD over HD in terms of patient outcomes and treatment satisfaction, at least as a short-term treatment. Based on the available evidence, the recent NICE Guideline on Peritoneal dialysis recommends offering all patients the choice of PD or HD if appropriate but that PD should be considered the first choice for adults with residual renal function and those without significant comorbidity (87)

3.5.3 What the future holds

Our data would suggest an ongoing decline in PD utilisation in Scotland, and clinician attitude and practice seems the most likely explanation for this. This attitude is not readily supported by outcome data, and the success of PD programmes in North East Asia would suggest that greater PD utilisation is possible in Scotland. With an ageing population and the success of assisted PD in France this PD modality could have an expanded role to facilitate PD in those without social support or too physically infirm or disabled to perform their own exchanges (59, 88).

Expanding the use of PD in elderly patients would be an appropriate response to an ageing RRT population for whom quality of life and not necessarily long term survival becomes the most important consideration. The French experience has demonstrated that the cost of assisted PD, even with private nurses providing assistance, is still lower than HD (88). In recent years assisted PD has been used for a few patients in Scotland and it remains to be seen whether there will be expansion of this option.

There is a need for improved PD training for Scottish nephrology trainees. This may need to be formalised, as the *ad hoc* training provided in previous generations was in an era of greater PD usage, and longer working hours which provided greater exposure to PD.

3.6 Conclusion

The decline of PD in Scotland is likely to continue unless steps are taken to increase PD utilisation. Using current evidence PD arguably should be offered to all patients without absolute contraindication, and the option of assisted PD considered if required. While clinicians' attitudes may be contributing to this decline, the lack of exposure to PD for the next generation of nephrologists will almost certainly continue the trend unless training addresses this deficiency. Based on data from outcome studies, by observing the demise of PD without attempting to intervene to change current practice we are likely to be doing a disservice to our patients.

Chapter 4

Peritoneal dialysis-associated peritonitis rates and outcomes in a national cohort are not improving in the post millennium period (2000-2007)

4. Peritoneal dialysis-associated peritonitis rates and outcomes in a national cohort are not improving in the post millennium (2000-2007)

4.1 Introduction

Peritoneal dialysis (PD) related peritonitis remains the leading cause of technique failure and a significant cause of morbidity among PD patients. Peritonitis damages the peritoneal membrane, interfering with its ultrafiltration and dialysis capacity which may be temporary or permanent (89, 90). Time to first peritonitis is a significant risk factor associated with PD technique survival (91). Despite improvements in PD, there remains an important background rate of peritonitis that has not improved in recent years. Peritonitis is often caused by skin bacteria via peri-luminal (via the PD catheter tunnel) or intra-luminal contamination. It may also result from transvisceral, transvaginal (rare) or haematogenous spread of organisms and the PD catheter can become colonised by bacteria creating a "biofilm" that repeatedly seeds the peritoneum with bacteria (92, 93).

Our understanding of PD peritonitis is limited by the quality and variety of published studies. Many are single-centre, from small, selected populations, using various connection techniques and methods of data analysis. Similarly, multi-centre reports are often from research centres or units with a special interest in PD. Consequently there is wide variation in the peritonitis rates in the literature. Results from multi-centre studies in the USA and Canada (1 episode every 32.7 and 27.6 patient months respectively), Austria (1 episode every 51 patient months), Hong Kong (1 episode every 36-45 months) and prolonged follow-up from a large single centre in Korea (1 episode every 30 months) (17-20) are better than rates achieved in large national UK PD populations (1 episode every 18.8 - 19.2 months) and Australia (1 episode every 19.4 months) (21-23). The relevance of an individual study's results to current practice in another unit or country is open for debate.

There are several methods of describing peritonitis rate, and each provides different, but complimentary information. The most common methods are: life table analysis or Cox proportional hazards regression from start of PD to first episode of peritonitis ("peritonitis-free survival") and Poisson-based regression analyses applied to number of infections per treatment time per patient (usually months between peritonitis episodes) (94, 95).

The Scottish Renal Registry (SRR) gathers data from all dialysis patients in Scotland from all ten adult renal units. No PD patients in this cohort are excluded from analysis and patients are easily traceable if they move between units. The renal units cover a range of urban and rural locations and deprivation categories and there is very little migration of patients outside Scotland. This creates an ideal environment to study clinical practice and outcomes over a prolonged period of time in a large **national** population that is representative of the full spectra of patient demographics.

In 2004 Kavanagh et al published peritonitis incidence and outcome data from the Scottish Renal Registry (1999-2002)(22). Since this study was published the International Society for Peritoneal Dialysis (ISPD) and the UK Renal Association (RA) have updated their peritonitis guidelines which are broadly similar (16, 96). The RA guidelines suggest the following minimum standards:

- Peritonitis rate less than one episode every 18 months of PD
- Primary cure rate over 80%
- Culture negative rate less than 20%

The study aim was to determine peritonitis incidence and outcomes in the Scottish PD population and to compare this to the clinical performance measures recommended in the guidelines (96).

4.2 Methods

All 10 adult renal units collect data prospectively relating to peritonitis, PD treatment failure and other clinical parameters for all PD patients in Scotland and this data is reported to the SRR 6-monthly. All audit data were in the form of hand-written forms, identifying patients by name only. By searching the SRR database we were able to match every patient to their unique SRR number which allowed us to access additional clinical details. This information was entered into a computer database for analysis. Patients can be reliably identified if they move between units and we do not have any duplicate registrations. Complete audit data from all patients for all units between 01/01/2000-31/12/2007 have been analysed for this study.

4.2.1 PD Technique

All units used the double-bag Y-tubing with flush before fill technique for CAPD. All units used luer-lock connections for APD and 8/10 used APD programs which included a flush before fill throughout most of study period. No units routinely used connect assist devices.

4.2.2 Definition and classification of peritonitis

An episode of peritonitis was defined as white cell count in PD effluent of >100 cells/mm^3 with >50% polymorphonuclear leukocytes. Units followed recommended culture methods. Organisms cultured were classified as coagulase negative *staphylococci* (CNS), *Staphylococcus* Aureus (SA), gram negative, fungal, "other or mixed", Methicillin-Resistant *Staphylococcus* Aureus (MRSA) or culture negative. Primary cure was defined as an initial response to antibiotic therapy (decrease in dialysis effluent fluid white cell count and clinical improvement by day 4 of treatment). Refractory peritonitis was defined as peritonitis that does not respond to antibiotic therapy and results in catheter removal.

Recurrent peritonitis was defined as an episode of peritonitis within 4 weeks of stopping antibiotics. Technique failure attributed to peritonitis was based upon the individual units reporting this as the cause of discontinuing PD. Patients who died within 4 weeks of the onset of peritonitis, were classified as patient deaths related to peritonitis even if the episode had responded to treatment (97).

4.2.3 The calculation of peritonitis rate

Prevalent and incident PD patients were used to describe peritonitis rates (months between peritonitis episodes), range of causative organisms and patient outcomes. Only incident patients have been used to calculate peritonitis-free survival. Peritonitis rates were calculated as the total number of patient months on PD divided by the number of episodes of peritonitis and expressed as the number of months between episodes and/or the number of episodes per year at risk. The rates were converted to events per patient-year for Poisson regression analysis (performed with help from NHS statistician Jan Kerssens) to test the difference between the groups (relative risk).

Peritonitis free survival (time to first episode of peritonitis) was calculated using the Kaplan Meier method for incident PD patients. Funnel plots with mean and standard deviations have been used to present individual units' data as this method incorporates the population size or number of peritonitis episodes and allows clearer comparisons between units. Where units were shown to be outliers, defined > 3 standard deviations from the mean, further analysis was performed using the Chi-square test.

4.4 Results

4.4.1 PD Population

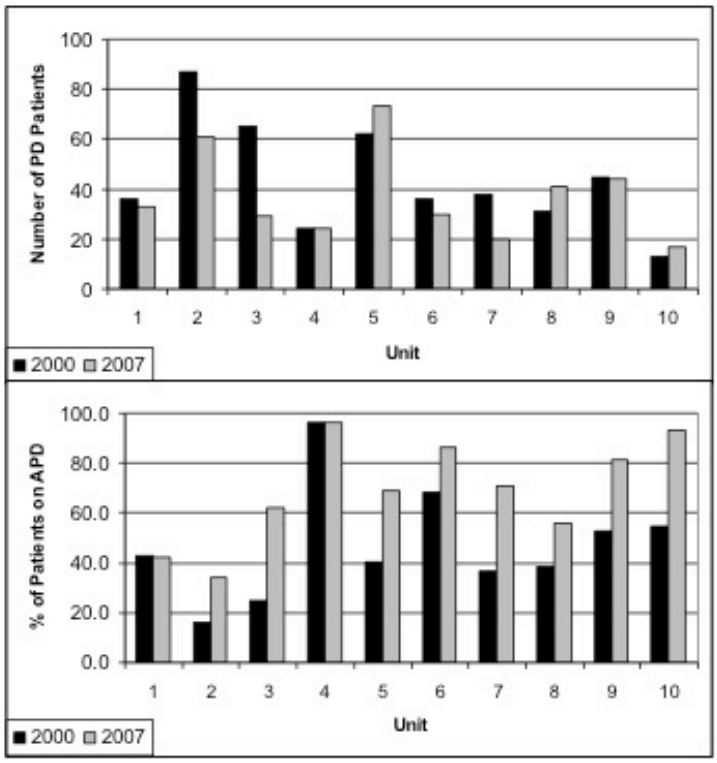
The prevalent RRT population in Scotland has increased between 2000-2007 with a corresponding increase in the proportion on hospital HD and a decrease in the proportion on PD. In 2000 there were 3210 patients; 48.2% with a functioning transplant, 35.6% on hospital HD, 10.1% on CAPD, 4.5% on APD, and 1.6% on home HD. By 2007 there were 4068 patients on RRT; 46.9% with a functioning transplant, 42.6% on hospital HD, 4.0% on CAPD, 5.4% on APD and 1.1% on home HD.

The number of incident patients starting RRT has remained constant with 560 patients in 2000 (72.1% HD, 25.9% PD and 2% transplant) and 570 patients in 2007 (75.3% HD, 21.4% PD and 3.3% transplant). No patients were on assisted APD during the study period.

The prevalent PD population in Scotland was 437 at the start of 2000 and 372 by end of 2007. The percentage of PD patients on APD in 2000 was 35%, increasing to 65% by the end of 2007 (figure 9).

The median age of the study population was 60 years (interquartile range 45-70 years), 60% were male, >95% were Caucasian, and approximately 20% had diabetes mellitus (DM) as their primary renal diagnosis.

Figure 9. PD Population and percentage of patients on APD by unit in 2000 and 2007.



4.4.2 Incidence

During the 8 year study period there were 1918 peritonitis episodes in 38,106 PD treatment months giving a national rate of 1 episode every 19.9 months (0.60 episodes per year at risk) in all incident and prevalent PD patients. The UK RA standard has been met at a national level every year 2000-2007 (figure 10) but appears to be stable rather than improving. Table 3 shows peritonitis rates worldwide, and our own data as comparison.

Figure 10. National PD peritonitis rate (months between peritonitis episodes) by year. The black dashed line represents the UK Renal Association minimum target of 1 episode every 18 months of PD.

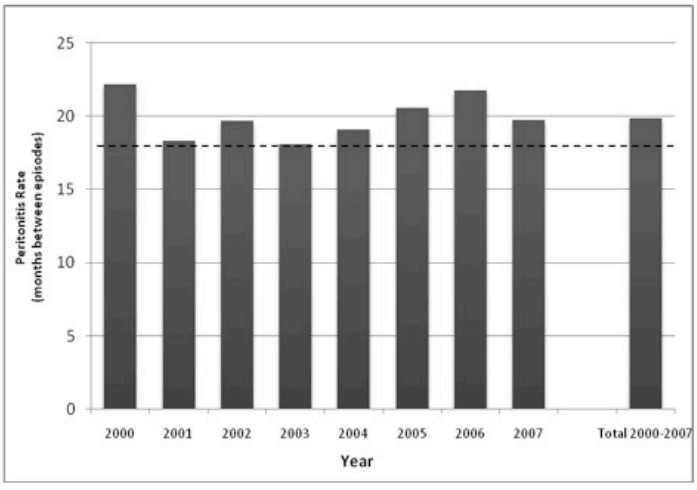
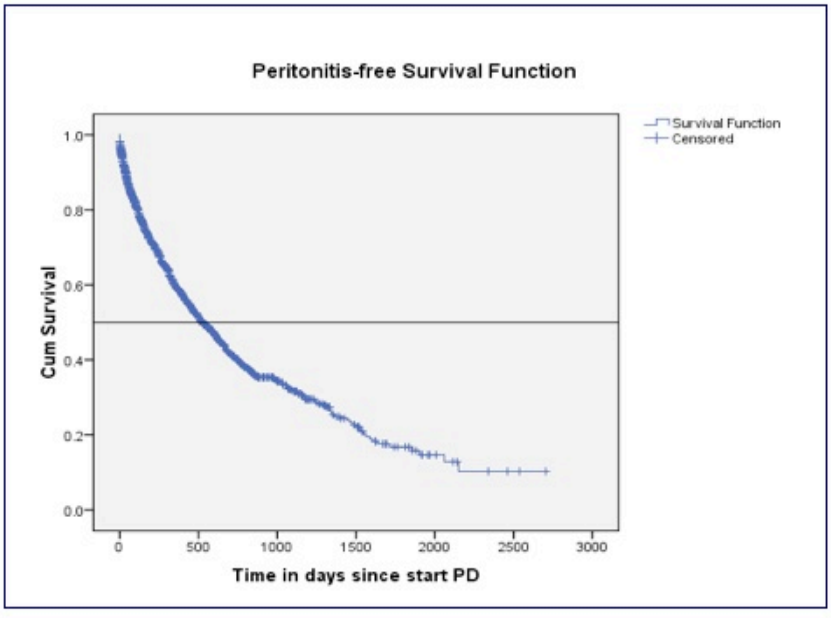


Table 3. Peritonitis rates in the published literature showing the higher rates in the UK, Australia and New Zealand, with much lower rates in North East Asia (adapted from reference (98)).

Country	Reference	Year	Population		Months between episodes	Episodes per year at risk
			Patients (n)	Centres (n)		
Brazil	Mores	2009	680		16.2	0.74
United Kingdom	Davenport	2009	1904 *patient years*		18.8	0.63
Scotland	Kavanagh	2004	1205		19.2	0.62
Australia/New Zealand	Fahim	2010	4675		19.3	0.62
Australia	Jarvis	2010	4675		19.9	0.60
Scotland	Brown	2011	1550		19.9	0.60
Netherlands	Ruger	2009	205		20	0.60
Canada	Mujais	2006		26	27.9	0.43
Portugal	Rodriques	2006	312		30.8	0.39
Spain	Perez-Fontan	2009	641		31.6	0.38
United States	Mujais	2006		35	32.4	0.37
Canada	Nessim	2009	4247		33.3	0.36
France	Castrale	2010	1631		33.3	0.36
Canada	Fang	2008	312		36.4	0.33
United States	Qamar	2009	137		50	0.24
Qatar	Shigidi	2010	241		50	0.24
Austria	Kipriva-Altfart	2009	332		51	0.24
Japan	Nakamoto	2006	139		54.5	0.22
China	Fang	2008	496		60	0.20
Taiwan	Tzen-Wen	2008	100		200	0.06

The median peritonitis-free survival, or time to first peritonitis, was 526 days (95% confidence interval 463 - 589 days) (figure 11). For the patients who developed peritonitis, the average number of episodes per patient was 2 (median = 1, IQR 1-2 episodes) and 54.5% of patients had only one episode.

Figure 11. National peritonitis-free survival censored for stopping PD or death.



When analysed by unit there was marked variation in peritonitis rate but it should be noted that there was marked variation in size of individual units and the proportion of patients on APD (figure 9). The peritonitis rate varied up to two-fold between units from an average of 1 episode every 15.3 months to 1 episode every 29.8 months (table 4). Seven of ten units met the RA target for peritonitis rate when averaged over 8 years (see *figure 12*) but only 3 of 10 units met the target every year.

Table 4. Peritonitis rate by unit and by organism cultured averaged over the 8 year study period and expressed as months between episodes and/or number of episodes per year at risk.

Unit	Months between episodes	Overall Rate for study period (episodes per year at risk)							
		Total	CNS	Gram Negative	SA	Fungal	Other	Culture Negative	MRSA
1	17.6	0.68	0.23	0.08	0.09	0.02	0.14	0.12	0.01
2	19.6	0.61	0.22	0.08	0.08	0.02	0.13	0.08	0.01
3	19.7	0.61	0.21	0.06	0.04	0.02	0.15	0.13	0.00
4	18.7	0.64	0.23	0.04	0.02	0.04	0.17	0.15	0.01
5	15.6	0.77	0.27	0.03	0.12	0.02	0.19	0.14	0.02
6	23.1	0.52	0.10	0.03	0.10	0.02	0.18	0.10	0.03
7	28.9	0.41	0.08	0.02	0.12	0.00	0.02	0.17	0.02
8	15.3	0.78	0.14	0.07	0.15	0.01	0.25	0.16	0.01
9	27.2	0.44	0.14	0.04	0.04	0.01	0.13	0.08	0.00
10	29.8	0.40	0.12	0.09	0.02	0.01	0.06	0.10	0.00
All Units	19.9	0.60	0.18	0.06	0.08	0.02	0.15	0.12	0.01

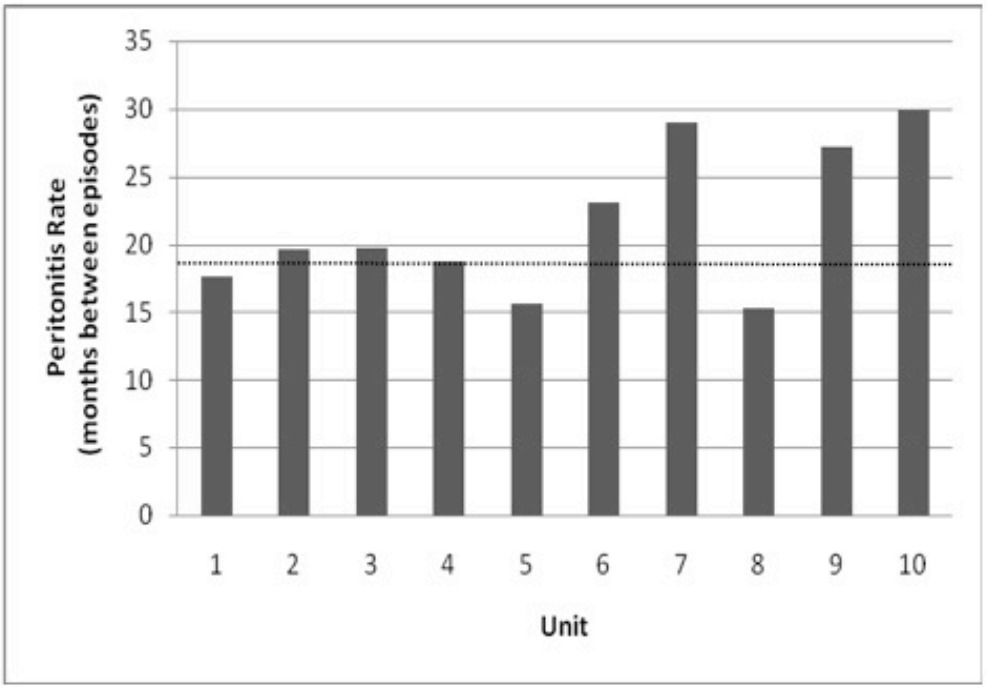


Figure 12. Peritonitis rate by unit averaged over 8 years of audit. Only 7 of the 10 units meet the UK Renal Association standard of less than one episode every 18 months (which is highlighted by the black dashed line).

There was no discernible, consistent improvement in peritonitis rates nationally or within units, but unit 5 has shown an increase in peritonitis rate in recent years (figure 13). The median peritonitis-free survival varied between units from 450 days and to more than 1000 days ($p<0.001$).

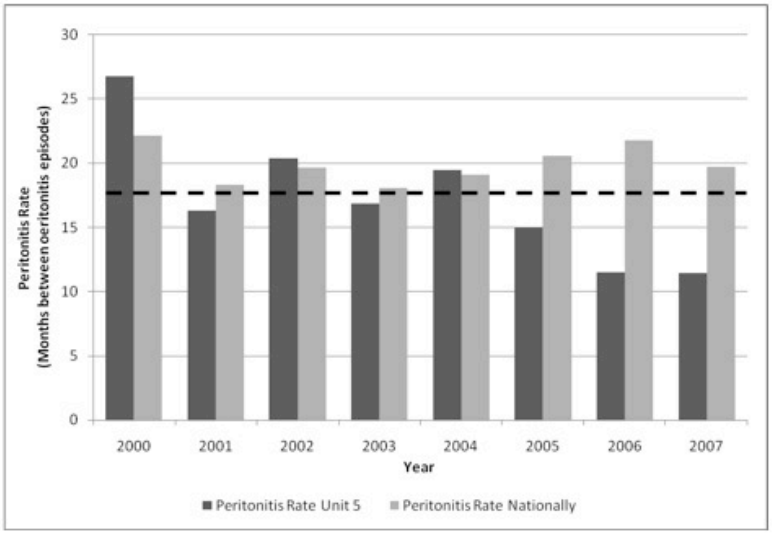


Figure 13. Peritonitis rate by year for unit 5 compared to national average showing increasing peritonitis rate for unit 5 in recent years (black dashed line represents UK Renal Association standard of less than one peritonitis episode every 18 months).

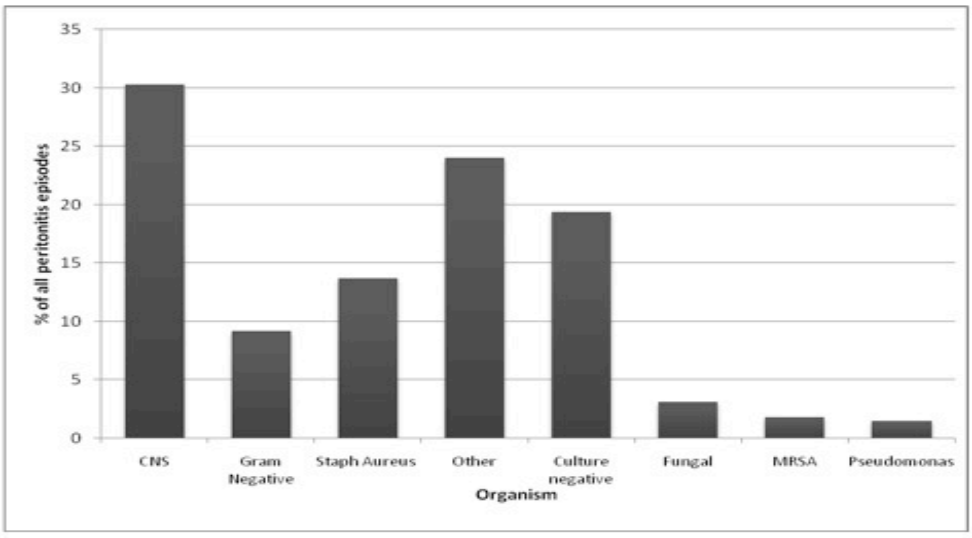
4.4.3 Peritonitis Rate on CAPD versus APD

The peritonitis rate was significantly higher for patients treated with CAPD at 1 episode every 17.6 months compared to APD at 1 episode every 22.3 months ($p<0.001$, RR=1.27). The median age at starting APD was 51.7 years (interquartile range (IQR) 37.8 – 63.1 years) and CAPD was 61.7 years (IQR 46.0 – 70.7 years). Consequently the median age at first peritonitis on APD was 55 years (IQR 41.1- 64.8 years) and on CAPD was 65 years (IQR 48.2 – 71.9 years). There were no differences in other recorded variables between APD and CAPD patients (gender, primary renal disease, presence of diabetes, deprivation scores, BMI).

4.4.4 Causative organisms

The causative organisms and rates of peritonitis in each unit are shown in table 4. Using data from all episodes from all units over the 8 year audit period, the percentages of different organisms cultured during peritonitis episodes are shown in *figure 14.* At 19.4%, the national culture negative rate meets the RA target of <20%. The relative proportion of each organism has not changed significantly over the 8 years of the audit. Despite concerns about increasing antibiotic resistance, there has been no increase in MRSA incidence over the audit period (1.8% of episodes overall). No episodes of extended spectrum beta lactamase (ESBL)-producing gram negative infections were reported.

Figure 14. Organisms cultured during all peritonitis episodes in Scotland 2000-2007 (expressed as percentage of total).



Between units and within units there was considerable variation in the frequency of specific organisms and the culture negative rate (*figures 15-17)*. With the variation in PD population and absolute numbers of peritonitis episodes, the percentage contribution of each organism may be misleading. Differences among the units are best displayed and analysed using funnel plots with the absolute number of episodes and percentage of total compared to the unit closest to the mean. Outlier units were identified if they were more than 3 standard deviations from the mean.

Figure 15. Culture negative peritonitis as percentage of all peritonitis episodes in each of the 10 renal units in Scotland 2000-2007.

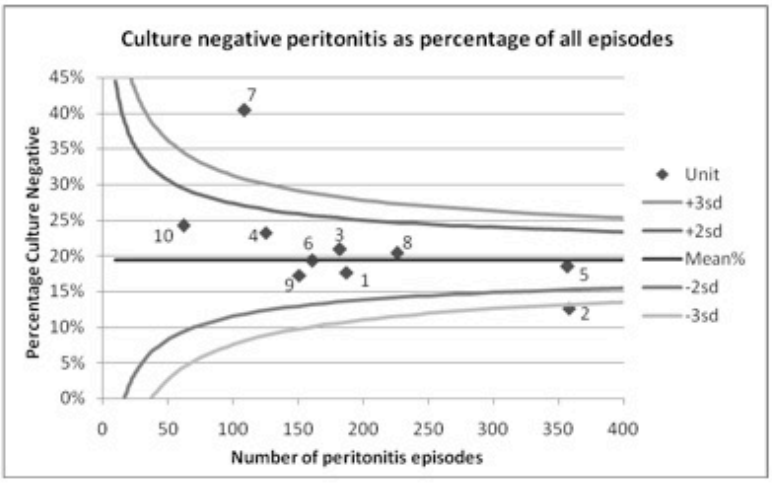


Figure 16. Staphylococcal aureus peritonitis as a percentage of all peritonitis episodes in each of the 10 renal units in Scotland 2000-2007.

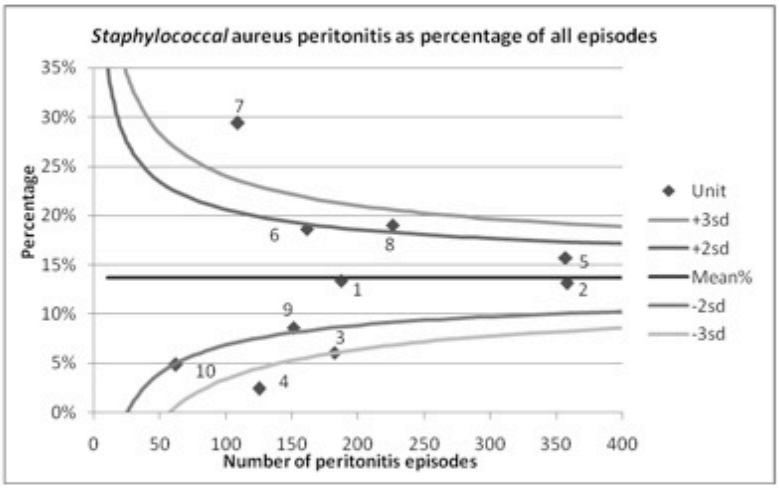
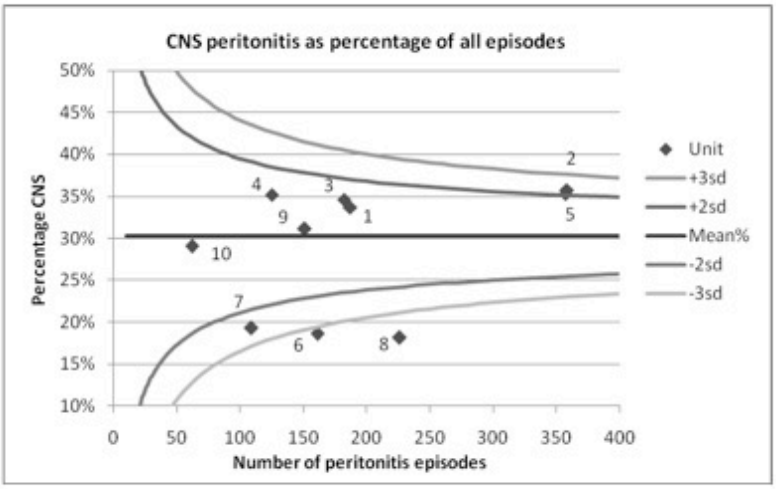


Figure 17. Coagulase negative staphylococcus peritonitis as a percentage of all peritonitis episodes in each of the 10 renal units in Scotland 2000-2007.



Using this method the only significant differences between the units were:

- The culture negative rates in unit 7 were significantly higher (42% compared to national average of 19.4% shown in *figure 15*) and this has remained a problem over the 8 year study period, although the absolute number of cases was small
- The rates of SA peritonitis were significantly higher in unit 7 but were improving (*figure 16*)
- The rate of CNS peritonitis was lower in units 6 and 8 (*figure 17*), and both units had higher than average rates of "other or mixed" organisms.

The causative organisms, including CNS, were similar for peritonitis episodes occurring on CAPD compared to APD.

4.4.5 Outcome

Nationally, the primary cure rate was 74.6 %, the refractory rate was 22.6%, and the death rate was 2.8%. 9.3% episodes were recurrences and 14.9% of peritonitis episodes resulted in technique failure over the 8-year audit period. Of all technique failures during the audit period, 43% were attributed to peritonitis.

Although all ten renal units have managed to achieve primary cure rates >80% in specific years, this has not been sustained, and the target has not been met at a national level. The national outcome and the outcomes within units have not changed significantly over the 8 years (*figures 18 and 19).*

Figure 18. National peritonitis outcomes during each year and the total audit period 2000-2007.

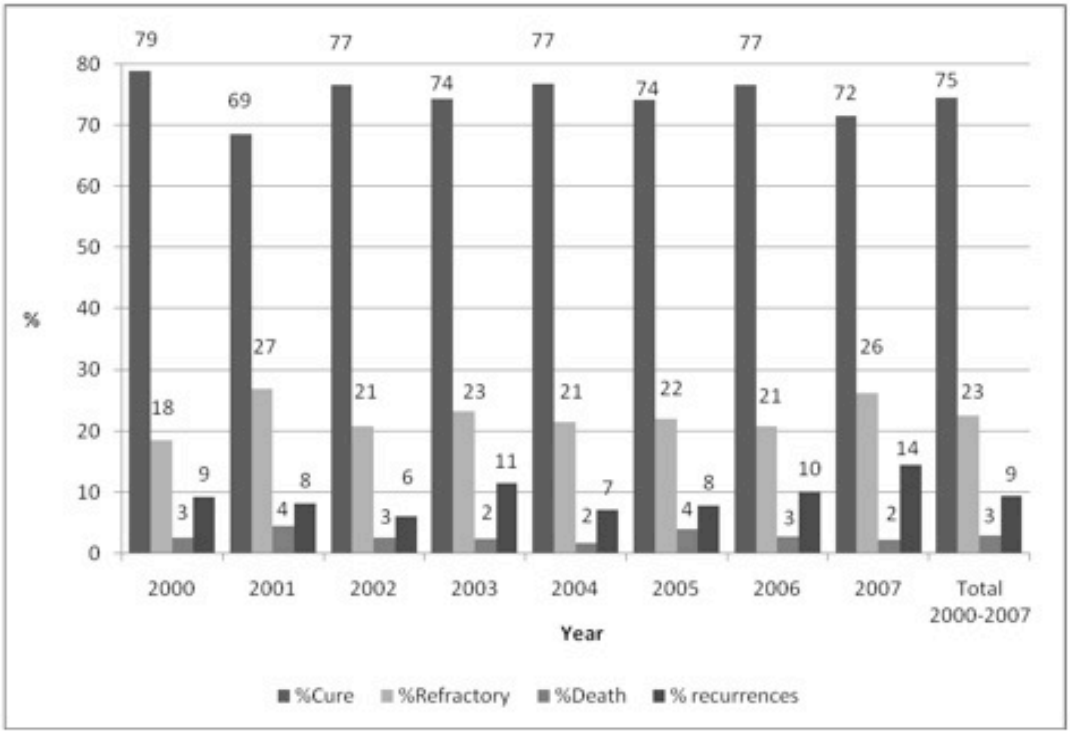
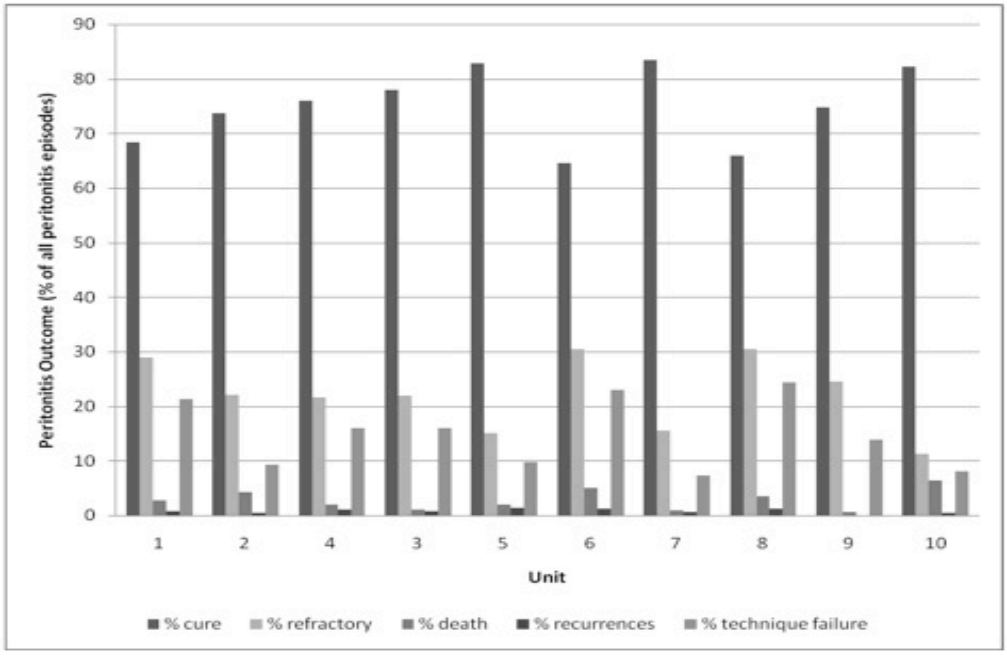
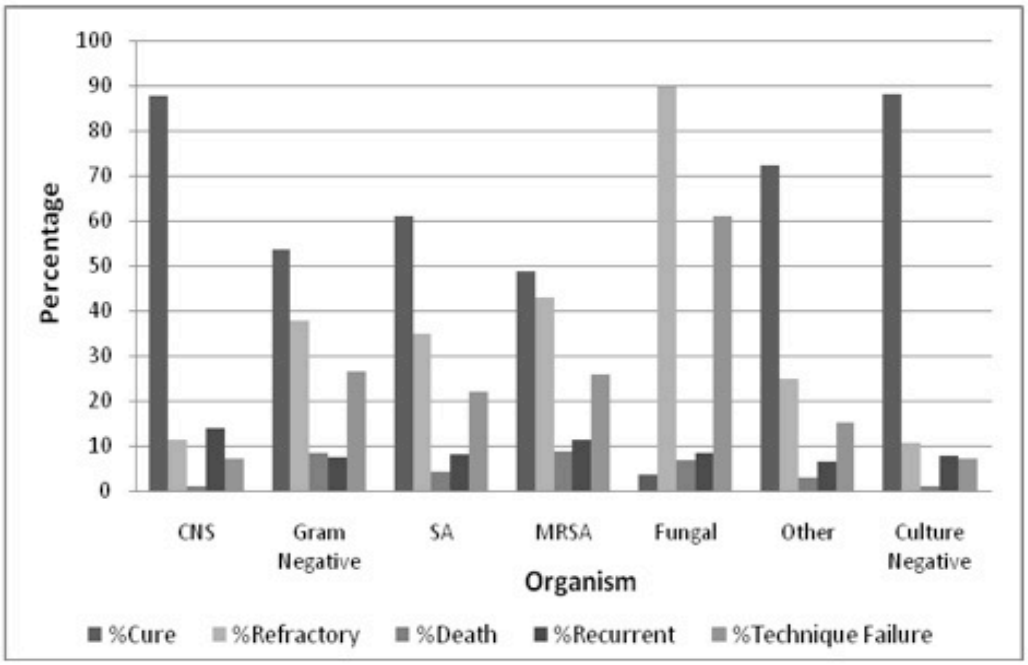


Figure 19. Peritonitis outcomes in each renal unit in Scotland 2000-2007. Only 3 of the 10 units have achieved a greater than 80% primary cure rate.



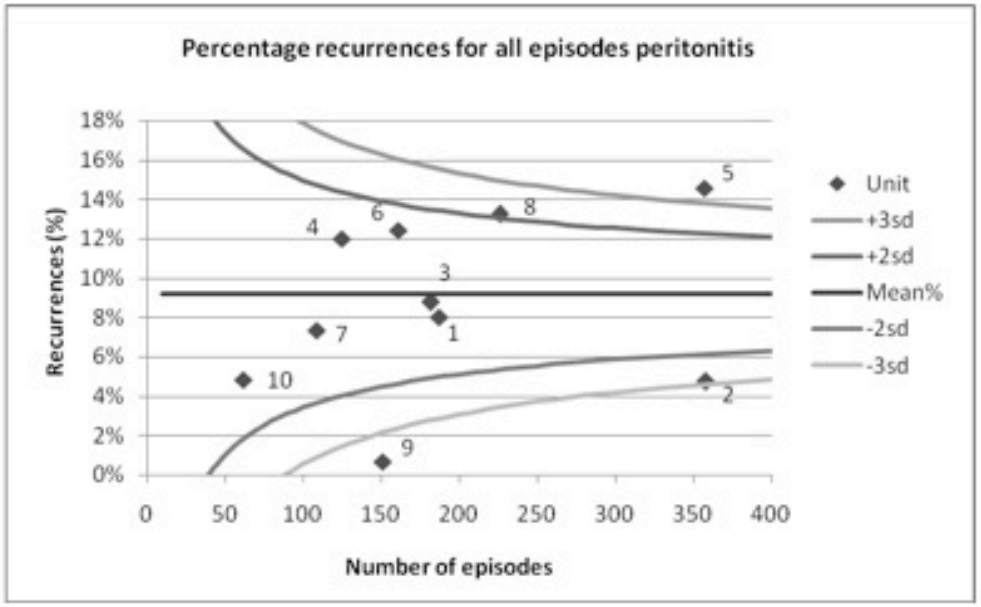
The outcome depended on the causative organism (*figure 20*) but outcomes due to specific organisms have been constant over the audit period. The proportion of different organisms cultured in each unit varied and this will influence outcomes and should be considered when examining differences between units. The units (6 and 8) with the lowest CNS rates have the lowest overall cure rates (65 and 66%).

Figure 20. Peritonitis outcome nationally 2000-2007 according to organism cultured.



The only significant difference between units in outcome is the higher rate of recurrences in unit 5 which has been an increasing problem in recent years (*figure 21*). This is the same unit that has seen higher peritonitis rates in recent years. The recurrence rates and outcomes of peritonitis were comparable for APD and CAPD in this audit.

Figure 21. Rate of recurrent peritonitis as a percentage of all episodes 2000-2007 by unit.



4.5 Discussion

National peritonitis rates in Scotland consistently met the RA standard of less than one peritonitis episode every 18 months, but there has been no convincing ongoing improvement. With complete data from all PD patients, covering the spectrum of patient demographic characteristics and geographical areas, the rate of 1 episode every 19.9 months represents current real-life PD practice in Scotland. Despite meeting the RA standard every year, the lack of convincing improvement in national peritonitis rates over the 8 year audit period raises the question as to whether rates are as low as they can be in a national PD cohort.

The peritonitis rate was comparable to the rate in the last Scottish audit of 1 episode every 19.2 months, Australian figures of 1 episode every 19.4 months, and the London, UK result of 1 episode every 18.8 months (21-23). These rates are better than New Zealand's rate of 1 episode every 15 months but higher than elsewhere in the world where rates are below 1 episode every 30-50 months illustrated in table 1 (17-20, 23). The median peritonitis-free survival for our cohort is 526 days or 17.3 months, which is comparable to Australian data (23) but shorter than a recent multi-centre study in the USA which quoted approximately 26 months (99).

It is likely that any further improvement in Scottish peritonitis rates would require a significant change in practice and/or adoption of any new technique if and when it becomes available. The Pittsburgh PD programme demonstrated impressive improvements in peritonitis rates (from 1 episode every 24 months to 1 episode every 48 months between 1990 and 2007) in response to several interventions including routine gentamicin exit site prophylaxis and patient re-training (100, 101).

Previous studies have shown similar improvements with major changes in PD practice including "aggressive patient re-training", but in an era when PD connectology devices were improving which may confound the results (102). In late 2004 the Scottish Renal Association held an educational meeting with representation from all renal units to discuss and reinforce current best practice in PD. There was no sustained improvement in PD peritonitis rates following this meeting.

When comparing individual units it is crucial to consider the size of the unit and spectrum of organisms cultured, particularly if focussing on short time intervals. We have overcome this by analysing data over a prolonged period, yet still within a time period where units are using currently recommended connectology and antibiotic protocols. Similarly, rather than over-interpreting small differences between units, we have focussed on the few clear differences when a unit's results on funnel plots are more than 3 standard deviations from the national average (figures 15-17 and 21). Using this method, one of the largest PD units in Scotland was found to have a rising incidence of peritonitis, with an increase in recurrent episodes. Further investigation revealed that haemodialysis spaces were limited in this unit such that patients needed to continue PD longer than the clinicians would necessarily have chosen and there was also a higher patient: PD nursing staff ratio. This highlights the importance of detailed long-term audit to identify problems, and provide evidence to help units lobby to improve their facilities.

4.5.1 Organism

The range of organisms causing peritonitis in our cohort reflects previously published series from the UK and elsewhere (21, 103, 104). In particular there has been no fall in the proportion of CNS peritonitis, which is thought to relate to touch contamination, and is the most curable of the organisms commonly causing peritonitis. There was no obvious reason

why 2 units have significantly lower rates of CNS peritonitis in terms of differences in PD population and they appear to have similar approaches to training and re-training compared to other units with higher rates. The units with lower peritonitis rates should be examined in more detail; for example, are they providing better training/re-training? Do they manage contamination differently?

4.5.2 Outcome

The outcomes of peritonitis in our audit reflect previously published data. Primary cure rates did not meet the UK RA standard of >80%. This has been a common theme in the literature, with recent studies quoting overall primary cure rates of 71.7% (London, UK), 78.2% (USA), and 78% (Australia) (17, 22, 23). Outcome relates directly to the organism causing peritonitis. We would expect the rates of CNS peritonitis to fall as PD technique improves to reduce touch or trans-catheter contamination. With 90% cure rates, and accounting for around 30% of peritonitis episodes, any fall in CNS rate will result in a fall in primary cure rates as other, less curable, organisms become proportionally more common. Similarly, units with high cure rates had higher rates of CNS peritonitis which may mean that less stringent catheter care could mean the unit is more likely to meet the audit standard for primary cure.

In our audit no single unit has met this standard every year, and only the smallest units have met it in individual years; the same units had cure rates <60% in other years, which suggests that this may not be an achievable target in the current era. In other words is a >80% primary cure rate for peritonitis still an appropriate or achievable standard in the modern era when the proportion of episodes due to CNS is lower? If we exclude all CNS peritonitis from our analysis, the overall cure rate for the other organisms combined was 68.9%, which suggests that a 70% cure rate would be more realistic minimum target.

Although only 14.9% of peritonitis episodes resulted in technique failure 43% of all technique failures in Scotland were attributed to peritonitis. This is similar to the rate in Japan (47%), London, UK (41.7%), but higher than Australia (29%) and New Zealand (30%) (21, 23, 105). Mortality relating to PD peritonitis varies from 3.5% - 6.7% in the literature whilst the rate was 2.8% in our audit (21, 106-108). However, the definition of peritonitis-related mortality varies between studies and so results may not be comparable. The refractory rate in this study was 22.6%. It is conceivable that a lower threshold for catheter removal may have had a positive effect on the mortality rate in this study.

However, catheter removal may also be a marker of peritonitis severity as demonstrated by Fontan's study which showed that the odds ratio of death was 12.9 in PD patients with peritonitis who had the catheter removed (108).

4.5.3 CAPD versus APD

From the literature it is not clear whether the modality of PD (APD or CAPD) influences the risk of peritonitis. Studies have suggested that APD has lower peritonitis rates (21, 109-111). Other studies have suggested that the risk is equivalent (22, 23). A large (>11,000 patients) multicentre study from the USA has shown that CAPD carries a higher risk (99). Possible reasons for the disparity between studies include, to varying degrees, insufficient study power, retrospective design, selected populations, short follow-up and in the older studies, differences in CAPD technique.

Our data show a convincing difference between CAPD and APD, with lower rates for patients using APD in a large, national population with prospectively gathered data over 8 years. However, analysis of the data demonstrated that patients starting CAPD and experiencing peritonitis on CAPD were older than those on APD. This may explain the observed difference in peritonitis rate as old age has been associated with a higher

peritonitis risk (0.52 vs 0.37 /patient-year for >70 and 40-70yrs respectively) (107, 112, 113) although more recent studies have shown no difference in peritonitis rates in older patients (114, 115).

Lower peritonitis rates in APD may reflect less risk of catheter contamination as fewer connect/disconnect procedures are required. The proportion of patients using APD increased significantly over the audit period and so a lower national rate of CNS infections and of peritonitis would have been expected and this was not the case.

4.6 Conclusion

The results reported in this large PD cohort reflect current "real life" PD practice in the UK. This national study shows that peritonitis remains the main cause of technique failure and is an important cause of patient morbidity and mortality in Scotland. The relatively static peritonitis rate over the 8 year study period, which is caused by the same wide range organisms, suggests that there may always be a "background" incidence of peritonitis that is not preventable but still leaves scope for improvement towards rates reported in other studies. We should first look to the units and countries with lower peritonitis rates to see if we can adopt any successful elements of their practice before resigning ourselves to our ongoing peritonitis burden.

Chapter 5

Risk factors for Peritoneal Dialysis-related peritonitis in the Scottish Population

5. Risk Factors for Peritoneal Dialysis-related Peritonitis in the Scottish Population

5.1 Introduction

Not every patient will experience peritoneal dialysis (PD) associated peritonitis, while some will suffer recurrent bouts with no identifiable reason for this. The risk factors for peritonitis, specific causative organisms, recurrent peritonitis, and outcomes of peritonitis are incompletely understood. The literature on this subject is often limited to small, single-centre or specialist unit observational studies that have provided conflicting results. It is debatable whether the results from one study population or unit are transferable to other units. There is a need for large, multi-centre, national trials to further delineate risk factors for peritonitis. Numerous potential risk factors have been considered:

5.1.1 Possible Risk Factors

Age.

Old age has been associated with a higher peritonitis risk (0.52 vs 0.37 /patient-year for >70 and 40-70yrs respectively) (112) but other studies have shown no difference (114, 115).

Body Mass Index (BMI)

In a registry based study including 10,709 patients over a 12 year period, obesity (BMI >25) was associated with shorter peritonitis-free survival, more frequent peritonitis episodes than patients with BMI 20-25 (116). Smaller studies have not found differences in peritonitis risk but have found obese patients (weighing >110% over ideal body weight) to be more likely to require catheter removal for persisting infection (117). Similarly, obese patients have been shown to be more at risk of exit site infections, which itself is a risk factor for peritonitis (118).

Diabetes Mellitus

Patients with diabetes mellitus have been shown to have increased risk of first peritonitis (HR 1.5, CI 1.05-2.4) and shorter peritonitis free survival (49 versus 82 months, p=0.002)(119).

APD versus CAPD

Theoretically peritonitis rates would be lower with APD as it requires fewer connection/disconnections than CAPD but studies present conflicting results. In Scotland, the Australia and New Zealand (ANZDATA) and a Canadian cohort, peritonitis rates for APD and CAPD were not significantly different (22, 115, 120). A large US study (12,000 patients) showed a *lower* rate of peritonitis for CAPD (RR 0.939, 95% CI 0.883-0.998) (99) but a recent multi-centre study in London showed a *higher* peritonitis rate with CAPD ($p<0.05$) (21).

Nutritional Status

Malnutrition has been associated with a higher rate of peritonitis, and shorter peritonitis free survival in the developing world (121). This and other small studies have shown that a low serum albumin at the start of PD is associated with higher risk of peritonitis. (119, 122-124).

Nasal Staphlococcus Aureus Carriage

Patients with nasal carriage of *staphloccocus aureus* (SA) have up to four-fold increased risk of developing SA exit site infections (125). The same study found that nasal carriers of SA did not have increased peritonitis per se, but the cases of SA occurred in patients with SA nasal carriage. Up to 77% of SA peritonitis occurs in SA nasal carriers and there is evidence that nasal mupirocin ointment can reduce the incidence of exit site infections and peritonitis (22, 126).

Residual Renal Function

Reduced residual renal function has been shown to be a risk factor for peritonitis, but this may relate to its interaction with nutritional status and serum albumin, which are also risk factors (124, 127).

Unit and Nursing Experience

There is evidence suggesting that units with a specialist PD interest, who generally have larger PD populations, have better peritonitis rates and outcomes but previously published multi-centre Scottish data and London data did not find significant differences between units (21, 22, 128). Nursing experience may impact upon peritonitis, and recent evidence suggests that patients trained by more experienced nurses (>15 years of training) experienced significantly less gram positive peritonitis compared to those trained by nurses with fewer years' experience (129).

PD Dialysate

There is no evidence that specific peritoneal dialysis solutions may be associated with a higher risk of infectious peritonitis, although there is little data looking at this. No difference in peritonitis rates has been demonstrated in studies examining use of conventional glucose based dialysis solutions versus Extraneal or Nutrineal (123, 130). A randomized controlled trial studying potential effects of biocompatible versus standard solutions found no benefit in terms of peritonitis rate (131). Icodextrin (Extraneal) has been associated with sterile peritonitis(132).

Socioeconomic status

There is no published data describing the effect of socioeconomic status or deprivation category on risk of peritonitis or poor outcome from peritonitis in the Western World. A Chinese study found that patients from more deprived groups had a higher risk and poorer outcomes of peritonitis (133).

Primary Renal Diagnosis (PRD)

There is no published evidence that specific PRD convey increased risk of PD peritonitis, with the exception of diabetes mellitus, as detailed above.

Psychological Factors

Depression is common in patients with end-stage renal disease and has been linked to increased risk of peritonitis in PD patients (134, 135). Whether screening for, and treating depression would impact upon peritonitis rates is yet to be established.

5.1.2 Variability in studies and outcome measures

The inconsistent results from different studies are likely to reflect, at least in part, differences in study populations and study design. In addition, peritonitis may be described as a rate ie months between episodes or episodes per year at risk (analysed using Poisson regression analysis) or as peritonitis-free survival (analysed using Cox proportional hazards modelling). The latter only examines the time to first peritonitis, and does not allow for recurrent episodes. Ideally both these measures should be analysed, as well as the rates of individual organisms, and the outcome of peritonitis.

5.2 Aim

The aim of this study was to identify factors in the Scottish PD population that may be associated with increased risk of PD peritonitis and/or poor outcome from peritonitis.

5.3 Methods

All 10 adult renal units collect data prospectively relating to details of all peritonitis episodes, PD treatment failure, PD adequacy and other clinical parameters for all PD patients in Scotland. This data is reported to the SRR 6-monthly as hand-written audit forms. Complete audit data from all **incident** patients for all units between 01/01/2000-31/12/2007 have been analysed for this study. Details of dialysis history, demographic data and relevant blood results were downloaded from the SRR database for all incident patients treated with PD between 01/01/2000-31/12/2007.

5.3.1 Definition of Peritonitis

An episode of peritonitis is defined as white cell count in PD effluent of >100 cells/mm^3 with >50% polymorphonuclear leukocytes. Organisms cultured were classified as coagulase negative *staphylococci* (CNS), *staphylococcus aureus* (SA), gram negative, fungal, "other or mixed", methicillin-resistant *staphylococcus aureus* (MRSA), culture negative or pseudomonas.

5.3.2 Definition of Peritonitis Outcome

Outcomes of peritonitis were based upon the standard definitions previously described in the literature. Primary cure includes response to antibiotic therapy with falling white cell count and clinical improvement by day 4. Refractory peritonitis was defined as peritonitis that does not respond to antibiotic therapy and results in catheter removal. Recurrent peritonitis was defined as an episode of peritonitis within 4 weeks of stopping antibiotics (prescribed for an episode of peritonitis). Technique failure refers only to technique failures attributed to peritonitis. This was based upon the individual units reporting peritonitis as the cause. Patient deaths included patients who died within 4 weeks of confirmed peritonitis, even if the episode had responded to treatment.

(The primary outcomes are considered to be cure, refractory or death and therefore an episode may be categorised as a recurrence but also be cured, or refractory and result in technique failure. This is important when viewing tables describing data as percentages whereby the total percentage may be >100.)

5.3.3 Data used for analysis

The following data (% of patients with data) are available for comparison for the incident PD population: age (100%), sex (100%), renal unit (100%), BMI (97.5%) at start of PD, primary renal diagnosis (PRD) (100%), Scottish index of multiple deprivation (SIMD2 2006) score (98.2%) and DM diagnosis or not (100%). SIMD2 is a deprivation score, whereby 1 is least deprived, 5 most deprived. The dialysis population in Scotland is >95% Caucasian (SRR report). Serum albumin concentration result less than 2 months before the start of PD was available for 1156 (87%) of patients. Adequacy results measured within 6 months of commencing PD were available for 1035 (78%) patients. Of those with no adequacy result, 96 (7.3%) patients were on PD for less than 6 months of whom 81 (6.1%) patients had PD for less than 3 months.

Details of SA nasal carriage, exit site prophylaxis and use of nasal mupirocin to eradicate SA carriage were not available for individual patients. However we were able to make comparisons between units that routinely use exit site prophylaxis and/or nasal SA eradication treatment. In the units using exit site prophylaxis the exact date that this became protocol is not known, but has been ongoing for several years. This must be borne in mind when interpreting the data. Details relating to PD dialysate type/brand were not available for enough patients to be worth including in our analysis. Similarly, peritoneal equilibration test (PET) results were not available for the majority of our patients.

We did not have details regarding exit site infection as the PD audit does not collect this data. We had no information relating to patients' psychological well-being or if there was any history of depression.

5.3.4 Statistical Analysis

Basic data are described either as mean and standard deviation, or median and interquartile range. For some analyses, which are clearly stated in the results, the data was split into clinically relevant categories as follows: age was split into 2 categories (<70 or ≥70 years), BMI into 4 categories (<20, 20-25, >25-30, >30), PRD into 5 categories (primary glomerulonephritis, interstitial nephropathies, multisystem diseases, diabetes mellitus, unknown or other), deprivation category was split into 5 categories (SIMD2 2006), and serum albumin 3 categories (<30, 30-34.9, ≥35 g/dl). RRF was initially split into 6 categories (<10, 10-29.9, 30-49.9, 50-69.9, ≥70 l/wk/1.73m^2 and unknown), but after initial analysis it was clear that the significant difference between the group was for patients with RRF <10l/wk/1.73m^2 and those with higher clearances. Much of the analysis of RRF is based on comparisons of patients with <10 and ≥10l/wk/1.73m^2. This is clearly stated in the results.

Statistical analyses were performed using SPSS version 19. Comparisons relating to time to first peritonitis between groups were analysed using Kaplan Meier Survival technique and the log rank test with p value <0.05 considered to be significant. Univariate analysis was performed to compare groups. For categorical variables Chi-squared analysis was performed. Otherwise ANOVA was used to compare means. If one factor appeared to be significant multi-variate analysis was performed using Cox regression analysis. For the purposes of Cox regression analysis the continuous data was analysed intact rather than split in to the groups detailed in the previous paragraph.

5.4 Results

5.4.1 Baseline Demographics

The total incident PD population during this period was 1324 patients. Of these, 668 patients (50.4%) experienced 1318 episodes of PD-related peritonitis during the audit period. The mean number of episodes per patient was 2 (median 1, IQR 1–2, range 1-12 episodes). Table 5 shows baseline characteristics of the population with respect to whether peritonitis was experienced or not. Patients experiencing PD peritonitis are more likely to be male and be older at the start of PD. Certain PD units (units 5 and 8) have a higher proportion of patients experiencing peritonitis.

Table 5. Comparison of baseline characteristics of PD patients who develop or do not develop peritonitis.

Variable	Peritonitis	No Peritonitis	P value
Male (%)	53.1	46.9	0.04
DM (%)	26.6	26.1	ns
Mean age (years ± SD)	55.7 ± 15.5	54.0 ± 16.0	0.05
Mean albumin (g/l ± SD)	35.0 ± 5.4	35.5 ± 5.2	ns
Mean RRF (l/wk/1.73m² ± SD)	52.8 ± 43.6	57.3 ± 39.8	ns
Mean BMI (kg/m² ± SD)	26.0 ± 4.7	26.1 ±5.1	ns
Unit (% of patients)			
1 (n=134)	48.5	51.5	
2 (n=308)	49.0	51.0	
3 (n= 84)	47.6	52.4	
4 (n=73)	41.1	58.9	
5 (n=231)	56.7	43.3	0.007
6 (n=130)	50.0	50.0	
7 (n=80)	48.8	51.2	
8 (n=125)	64.0	36.0	
9 (n=96)	46.9	53.1	
10 (n=63)	34.9	65.1	
SIMD2 Score (% of patients)			
1	16.0	17.6	
2	20.1	21.3	
3	22.4	24.1	ns
4	21.3	20.4	
5	20.2	16.6	
PRD (% of patients)			
Primary GN	16.3	19.4	
Interstitial Nephropathies	27.2	25.6	
Multisystem disease	18.3	18.4	ns
Diabetic nephropathy	19.9	20.7	
Not known or other	18.3	15.9	

Mean age, albumin and BMI refer to these measurements at the start, or as close to the start of PD (residual renal function (RRF)) as possible. Primary GN = glomerulonephritis.

5.4.2 Potentially Modifiable Risk Factors Relating to PD Practice

5.4.2.1 Unit

Risk of Peritonitis

There are significant differences between the 10 renal units in PD population as well as many of the baseline demographics and potential risk factors for peritonitis illustrated in table 6. There is no difference in mean PD exposure between units.

Table 6. Comparison of baseline characteristics of potential risk factors for PD peritonitis in renal units in Scotland.

	Unit										
Factor	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	***P value***
Mean PD Population[α]	34	72	37	24	57	37	32	35	43	19	*0.000*
SD (±)	5.1	8.3	11.2	4.1	10.5	8.3	6.6	5.3	3.8	5.6	
Total PD Population[β]	134	308	84	73	231	130	80	125	96	63	*0.000*
% Male	55.2	55.8	52.4	41.1	51.1	52.3	50.0	56.8	63.5	71.4	*0.03*
% DM[δ]	25.4	25.0	31.0	21.9	27.0	29.2	39.0	18.5	22.9	31.7	*ns*
% APD	33.2	34.0	47.9	94.0	50.9	79.4	50.4	43.6	65.6	81.8	*0.000*
Mean Age [γ]	51.6	53.0	57.0	55.4	53.2	57.7	52.8	58.5	55.9	61.9	*0.000*
SD (±)	15.9	16.0	14.1	16.4	15.8	15.6	14.5	15.7	14.2	16.1	
Mean Albumin[γ] **(g/l)**	37.2	36.1	33.0	36.1	35.3	36.4	35.5	30.5	35.1	35.7	*0.000*
SD (±)	4.8	5.4	5.2	4.3	4.9	4.6	5.1	4.9	4.4	5.6	
Mean RRF[γ] **(l/wk/1.73m²)**	63.6	42.9	49.2	62.5	64.3	66.6	63.1	47.9	42.4	64.5	*0.000*
SD (±)	42.3	35.1	35.7	38.4	57.0	45.1	41.1	32.8	25.6	35.1	
Mean BMI[γ] **(kg/m²)**	25.02	25.51	26.12	25.97	26.13	27.48	26.72	25.71	27.03	26.84	*0.009*
SD (±)	4.2	4.6	4.6	4.9	5.5	5.0	5.0	4.6	5.7	5.2	
SIMD Category **1**	24.8	17.6	15.0	11.1	23.2	17.8	11.5	8.1	15.1	4.8	
(%PD population) **2**	21.8	15.0	12.5	22.2	20.6	38.0	20.5	22.0	17.2	22.2	
3	36.1	19.3	11.3	22.2	20.6	18.6	23.1	35.0	15.1	39.7	*0.000*
4	11.3	24.9	22.5	20.8	17.5	12.4	21.8	26.8	10.7	20.6	
5	6.0	23.3	38.8	23.6	18.0	13.2	23.1	8.1	8.3	12.7	
PRD (n)											
Primary GN	30	49	13	12	42	23	14	27	15	11	
Interst. Nephrop.	28	93	24	16	65	26	17	39	30	12	
Multisystem Dis.	20	54	11	14	44	36	8	25	17	14	
DN	31	55	21	14	42	32	27	17	15	15	*ns*
Unknown	25	57	15	17	38	13	14	17	19	11	

[α]Mean PD population refers to the mean population over the study period. [β] Total PD population refers to all patients on PD over the study period. [γ] Mean age, albumin, residual renal function (RRF), and body mass index (BMI) refers to these measurements at the start of PD. [δ] DM=diabetes mellitus as primary renal diagnosis (PRD) or as co-morbid diagnosis.

There is a significant difference in the risk of developing peritonitis in one renal unit (unit 8) in Scotland. Figure 22 shows that unit 8 is an outlier, with 65% of incident PD patients experiencing at least one episode of peritonitis, >3 standard deviations away from the mean.

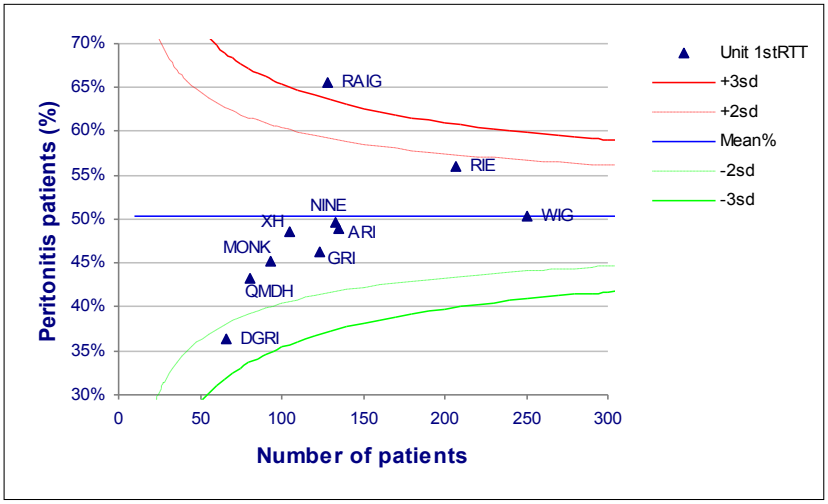


Figure 22. Funnel plot showing proportion of patients in each PD unit who have experienced peritonitis, with the mean and standard deviations plotted for reference. ***(Unit codes: ARI=1, WIG=2, GRI=3, QMDH=4, RIE=5, Nine=6, Monk=7, Raig=8, XH=9,DGRI=10)***

Peritonitis-free Survival

There is no difference between units in the time to first peritonitis (figure 23).

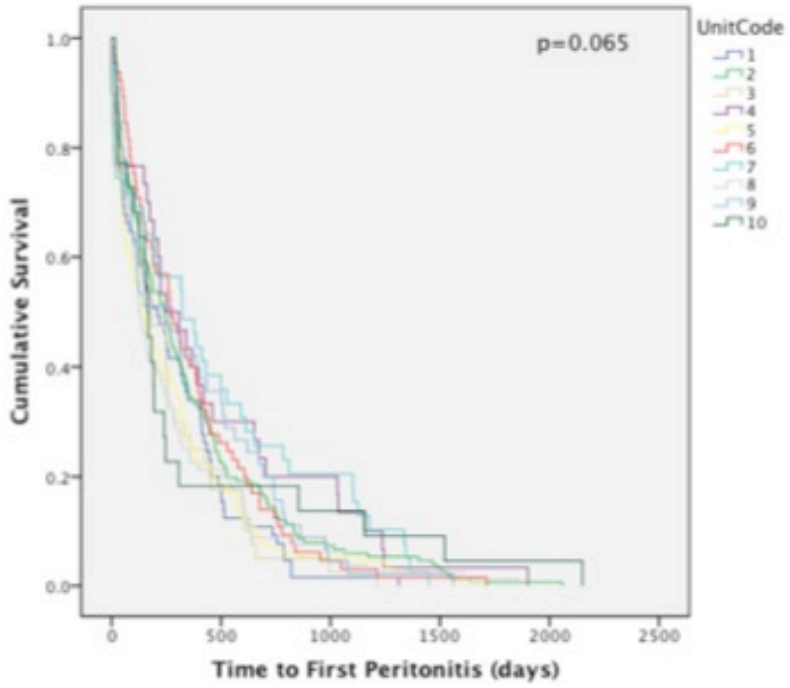


Figure 23. Survival plot showing the time to first peritonitis according to PD unit.

5.4.2.2 Unit Protocols, Unit Changes during the Study Period

Over the study period there have been changes in the PD population and in the nurse to patient ratios in the different PD units. Similarly, the units have different policies with respect to first line antibiotic therapy (i.e. pre-PD dialysate culture results), SA nasal eradication and exit site prophylaxis shown in table 7.

Table 7. Details of PD population, APD usage, nursing numbers and unit protocols comparing 2000 to 2007 to illustrate changes in these factors during the study period.

Unit	PD Patients (n)		APD (%)		Nurse:Patient Ratio[a]		1st Line Antibiotic Therapy		SA Eradication	
	2000	2007	2000	2007	2000	2007	Gram Positive	Gram Negative	Exit Site	Nasal
1	36	33	42.9	42.4	1:12	1:14	V[b]	[c]	Yes	Yes
2	87	61	16.0	34.5	1:29	1:17	V	C	No	Yes
3	65	29	24.8	62.1	1:30	1:10	V	C	No	Yes
4	24	24	96.1	96.3	1:20	1:13	V	Ci	No	Yes
5	62	73	40.3	68.7	1:15	1:16	V	Ci	Yes	Yes
6	36	30	68.6	86.3	1:15	1:9	V	C	No	Yes
7	38	20	36.7	70.7	1:22	1:6	V	C	No	Yes
8	31	41	38.7	56.1	1:10	1:6	V	Ci or C	Yes	No
9	45	44	52.6	81.2	1:17	1:16	V	G	No	Yes
10	13	17	54.8	93.3	1:7	1:9	V	C	No	Yes

[a]Nurse:Patient ratio refers to trained PD nurses and does not include auxillary or care worker input. [b]V= IP vancomycin, C = IP ceftazidime, Ci = oral ciprofloxacin, G = IP gentamicin. [c]This unit does not give empirical gram negative cover, only if gram negative organisms on gram stain/culture (antibiotic decided on individual patient basis).

5.4.2.3 APD versus CAPD

Risk of Peritonitis

Table 8 shows the differences in baseline characteristics when the cohort is divided according to whether the patients were on CAPD or APD at first peritonitis, and those who did not experience peritonitis. CAPD patients are younger and have a lower albumin.

Table 8. Comparison of baseline characteristics of patients experiencing their first peritonitis on APD or CAPD and those who did not experience peritonitis.

Variable	APD (n=307)	CAPD (n=360)	No Peritonitis (n=657)	*P value*
% Male	59.3	56.1	51.7	ns
% DM	26.3	26.8	26.1	ns
Mean age (yrs ± SD)	58.5 ± 15.3	52.5 ± 15.1	54.0 ± 16	<0.001
Mean Albumin (g/l ± SD)	35.5 ± 4.8	34.6 ± 5.8	35.5 ± 5.2	0.03
Mean RRF (l/wk/1.73m² ± SD)	53.3 ± 38.6	52.3 ± 47.9	57.3 ± 39.8	ns
Mean BMI (kg/m² ± SD)	26.4 ±4.7	25.7 ± 4.7	26.1 ± 5.1	ns
PRD (n)				
Primary GN	51	58	127	
Interst. Nephrop.	95	86	168	
Multisystem Dis.	48	74	121	ns
DN	64	69	136	
Unknown	49	73	104	
Unit (n)				
1	24	41	69	
2	49	102	157	
3	20	20	44	
4	26	4	43	
5	64	66	100	0.01
6	45	20	65	
7	12	27	41	
8	23	57	45	
9	28	17	51	
10	16	6	41	

Peritonitis-free Survival

The time to first peritonitis is significantly lower for CAPD than APD with a median 337 (291.0 – 383.0) versus 100 (77.5 -122.4) days (p<0.001) shown in figure 24.

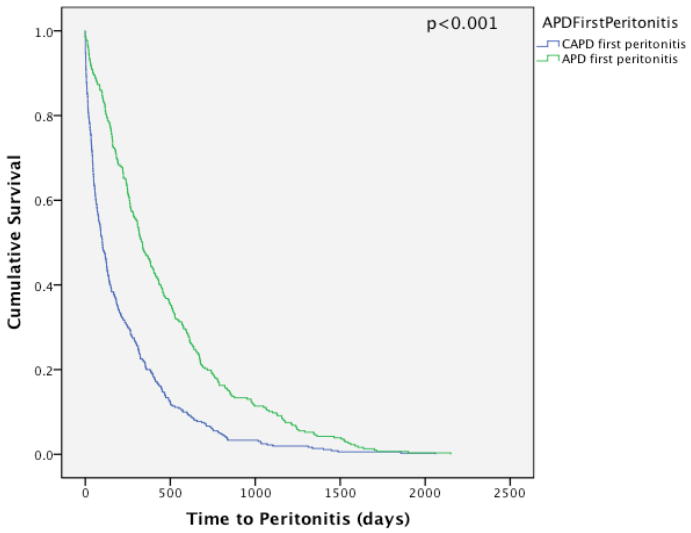


Figure 24. Time to first peritonitis comparing those on APD and those on CAPD.

5.4.2.4 Important Changes in PD Population during the Study Period

The PD population in Scotland has changed during the study period whereby most patients in 2000 (62.7%) were on CAPD, while in 2007 most (73.4%) were on APD (SRR data). There have been no changes in connectology or PD technique in Scotland during this study period. There is no difference in causative organisms, or outcome of peritonitis in those on APD versus CAPD at the time of infection.

5.4.2.5 Exit Site Prophylaxis (Mupirocin ointment)

Three of 10 units use mupirocin ointment empirically, and the other 7 units will use it for specific patients who experience recurrent peritonitis. Our data are limited by not having patient-specific data, and uncertainty as to the date when exit site prophylaxis became routine in the units using it. Our data suggests that the units using exit site prophylaxis have higher rates of SA peritonitis and no difference in recurrence rates (13.1 versus 8.4% of peritonitis episodes, p=0.01). There is no difference in mean SA rates, recurrence rates or other outcome measures. Examining the rate of SA peritonitis per year by unit, there is no obvious reduction in SA rates later in the study period. It is possible that these units have started using exit site prophylaxis in response to a higher SA peritonitis rate. Rates and outcome of other causative organisms are comparable.

5.4.2.6 Antibiotic Protocol

All units use intra-peritoneal (IP) vancomycin as first line/empirical therapy for gram positive cover (table 9). Antibiotic protocols suggested in ISPD and RA guidelines must include gram positive and negative cover as part of empirical therapy.

However unit 1 is not following this and omits gram negative cover pending culture results; it has the highest refractory outcome rate and technique failure rate for gram negative peritonitis. Three units (4,5,8) used ciprofloxacin as first line during the study period.

Table 9. Outcome of gram negative peritonitis according to units' first line ("blind") antibiotic therapy.

		Empirical Antibiotic therapy for Gram negative peritonitis				
Outcome of gram negative peritonitis	**Total All Units**	**None**	**Ceftazidime (IP)**	**Ciprofloxacin (PO)**	**Gentamicin (IP)**	***P value***
Number of cases	121	15	67	29	10	-
Cure (%)	53.7	27.1	60.2	54.9	47.3	0.001
Refractory (%)	38.0	68.2	27.9	43.3	46.8	0.001
Relapse (%)	7.4	5.2	4.1	18.9	0.0	0.001
Death (%)	8.3	5.1	11.9	2.2	7.1	0.01
Technique Failure (%)	27.2	55.4	13.1	45.3	19.7	0.001

Although the numbers of cases are small, table 9 suggests that ceftazidime therapy is associated with the highest cure rate, lowest refractory rate and lowest rate of technique failure. There are no other significant differences in organism or outcome when the data are analysed according to antibiotic protocol.

5.4.2.7 SA eradication

All units except one will swab patients' noses prior to PD catheter insertion and give at least 5 days treatment with topical SA eradiation therapy (mupirocin in 7 units, chlorhexidine in 2 units) to those patients who have nasal SA colonisation. Comparing the units that give eradication therapy to the unit that does not, SA rates are lower (13% versus 19%, p=0.02), SA recurrence rates are lower (7% versus 12%, p= ns), and technique failure rates attributed to the SA peritonitis are lower (18% versus 42%, p=0.001). There is no difference in the rate of MRSA or other organisms, or outcomes for these organisms.

5.4.3 Non-Modifiable Risk Factors: Patient-related Features

5.4.3.1 Gender

On univariate analysis more males than females had experienced peritonitis (53.1% versus 47.1%, p=0.029) but this was not significant on regression analysis.

5.4.3.2 Age

Risk of Peritonitis

Differences in baseline characteristics, causative organisms and peritonitis outcome are shown in table 10 comparing patients >70 to those <70 years at the start of PD. Patients > 70 years who develop peritonitis are more likely to have gram negative or "other"/mixed organisms and less likely to have CNS peritonitis. In keeping with the higher rate of less curable organisms in the >70 year olds, they are less likely to be cured and more likely to die from peritonitis.

Table 10. Differences in baseline characteristics, causative organisms and outcome of peritonitis according to age > or < 70 years

Variable	Age < 70 years (n= 1073)	Age ≥ 70 years (n= 251)	P value
Patients experiencing peritonitis (n)	535 (49.9%)	133 (53.0%)	ns
Total peritonitis Episodes (n)	1062	256	-
Male (%)	53.4	59.4	0.05
DM (*n* and %)	290 (27.0%)	58 (23.1)	ns
APD (% at first peritonitis)	31.6	49.7	0.000
Mean serum albumin (g/l ± SD)	35.7 ± 5.1	33.3 ± 5.5	0.000
Mean RRF at start PD (l/wk/1.73m² ± SD)	56.7 ± 42.8	45.8 ± 36.3	0.002
Mean BMI (kg/m² ± SD)	26.2 ±5.0	25.4 ± 4.2	0.05
Organism			
CNS (%)	322 (30.3)	59 (23.3)	0.02
Gram Negative (%)	89 (8.4)	32 (12.5)	0.05
SA (%)	148 (13.9)	30 (11.7)	ns
MRSA (%)	18 (1.7)	6 (2.3)	ns
Fungal (%)	25 (2.4)	7 (2.7)	ns
Other (%)	250 (23.5)	81 (31.6)	0.008
Pseudomonas (%)	14 (1.3)	7 (2.7)	ns
Culture Negative (%)	228 (21.5)	47 (18.4)	ns
Peritonitis Outcome			
Cure	821 (77.3)	178 (69.5)	0.01
Refractory	227 (21.4)	61 (23.8)	ns
Relapse	103 (9.7)	21 (8.2)	ns
Death	14 (1.3)	17 (6.6)	0.0001
Technique Failure	152 (14.3)	40 (15.6)	ns

Peritonitis-free Survival

Patients >70 years old at start of PD have significantly shorter peritonitis-free survival (median 152.0 days versus 219.0 days for those under 70 years, p=0.008)(figure 25).

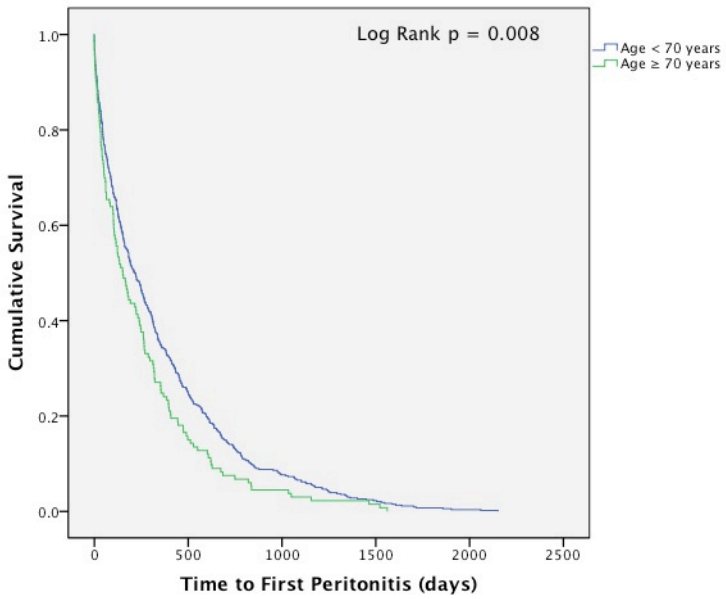


Figure 25. Kaplan Meier plot showing peritonitis free survival for PD patients <70 and >70 years old.

5.4.3.3 BMI and Primary Renal Diagnosis

There is no difference in the risk of peritonitis, peritonitis-free survival, number of peritonitis episodes, spread of organisms, or peritonitis outcome for different BMI categories or PRD (analysed by individual primary renal diagnosis (PRD) and by PRD groups as described in the methods section) except diabetes mellitus.

5.4.3.4 Diabetes Mellitus

Risk of Peritonitis

Of the incident PD population, 26.5% have diabetes mellitus as their primary renal diagnosis (20%) or as co-morbidity. Table 11 shows that diabetics in our population tend to have a higher BMI, higher RRF and lower mean albumin at the start of PD.

Table 11. Comparison of baseline characteristics and peritonitis episodes in diabetic and non-diabetic patients.

Variable	Diabetic (n= 348)	Not Diabetic (n=976)	P value
Patients experiencing peritonitis (n and %)	177 (50.9)	492 (50.4)	ns
Total peritonitis episodes (n)	345	973	-
Male (%)	53.7	54.9	ns
APD at first peritonitis (%)	45.8	46.2	ns
Mean age at start of PD (years ± SD)	55.7 (15.8)	54.6 (16.3)	ns
Mean albumin at start of PD (g/l ± SD)	34.3 (5.3)	35.6 (5.3)	0.001
Mean RRF at start of PD (l/wk/1.73m^2 ± SD)	60.5 (43.4)	53.0 (41.3)	0.01
Mean BMI at start of PD (kg/m^2 ± SD)	27.6 (5.1)	25.6 (4.7)	0.000
Deprivation score (SIMD2) (n and % patients)			
1	44 (12.7)	174 (18.2)	
2	72 (20.8)	197 (20.6)	
3	78 (22.5)	224 (23.5)	ns
4	83 (24.0)	188 (19.7)	
5	69 (19.9)	171 (17.9)	
Organism causing peritonitis (n and %)			
CNS	93 (27.0)	288 (29.6)	ns
Gram negative	24 (7.0)	97 (10.0)	ns
SA	62 (18.0)	116 (11.9)	0.006
MRSA	9 (2.6)	15 (1.5)	ns
Fungal	8 (2.3)	24 (2.5)	ns
Other	79 (22.9)	252 (25.9)	ns
Pseudomonas	7 (2.0)	14 (1.4)	ns
Culture Negative	79 (22.9)	777 (20.1)	ns
Peritonitis Outcome (% of episodes)			
Cure	90 (73.9)	744 (76.5)	ns
Refractory	82 (23.8)	206 (21.2)	ns
Relapse	51 (14.8)	73 (7.5)	0.0001
Death	8 (2.3)	23 (2.4)	ns
Technique Failure	52 (15.1)	140 (14.4)	ns

A higher proportion of diabetics suffer SA peritonitis (Chi-square p=0.006). On logistic regression analysis incorporating DM, age, serum albumin, BMI, and RRF, DM is the only significant predictor of SA peritonitis (HR 1.84 (1.2-2.9) p=0.01). Diabetics have significantly higher rate of peritonitis recurrence (Chi square p=0.0001). On logistic regression analysis DM (HR 2.1 (1.3-3.3) p=0.003) but also serum albumin (HR 1.1 (1.02-1.10) p=0.01) are predictors of recurrence of peritonitis. Otherwise causative organisms and outcomes are comparable between diabetics and non-diabetics.

Peritonitis-Free Survival

There is a trend toward shorter peritonitis-free survival in diabetics versus non-diabetics (median 161.0 days (102.7-219.3) versus 219.0 days (181.6-256.4), p=0.07). When the cohort is further subdivided by gender, there is a significantly shorter peritonitis free survival in diabetic compared to non-diabetic females (median 138.0 days (87.4-188.6) versus 224.0 days (155.9-292.4) p=0.05). This is not apparent in diabetic versus non-diabetic males (median 192.0 days (100.7-283.3) versus 192.0 (139.3-244.7), p=0.44) (figure 26).

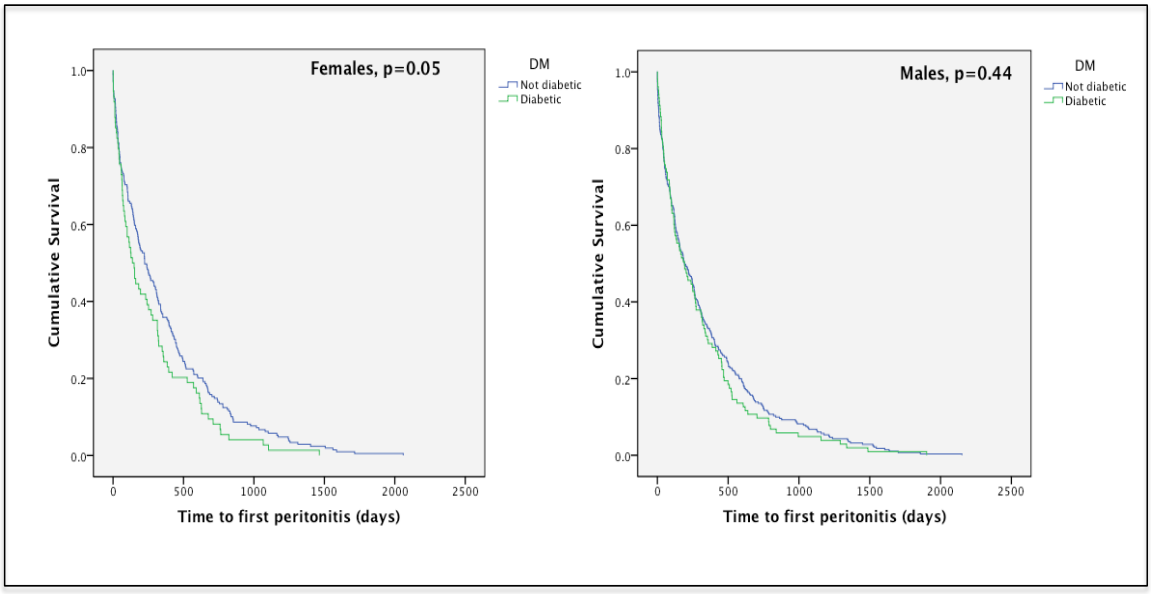


Figure 26. Kaplan Meier plots for peritonitis free survival comparing males and females with or without diabetes.

On further analysis, diabetic females have a significantly lower mean albumin than non-diabetic females (33.8 ± 5.6 versus 35.3 ± 5.5, p=0.006). Otherwise diabetic versus non-diabetic females are comparable with respect to other variables.

5.4.3.5 Serum Albumin

Risk of peritonitis

The normal range for the assays used in Scotland is serum albumin ≥ 35 g/l. Patients with serum albumin <30 g/l are more likely to be female, diabetic, have lower RRF, a lower BMI and be older at the start of PD (table 12). Patients with higher serum albumin develop more CNS peritonitis (p=0.000), whilst those with lowest serum albumin experience more gram negative peritonitis (p=0.008). On logistic regression analysis incorporating serum albumin, sex, DM, RRF, BMI and age at start of PD there is no relationship between serum albumin (or the other factors) and specific organisms. However, serum albumin does predict peritonitis recurrence (HR 1.1 (1.02-1.10) p=0.01) along with DM.

Table 12. Comparison between groups according to serum albumin at the start of PD.

	Serum Albumin Concentration (g/l)			
Variable	**< 30 (n= 163)**	**30 - 35 (n= 390)**	**>35 (n= 603)**	**P value**
Patients experiencing peritonitis (n/%)	89 (54.6)	210 (53.8)	299 (49.6)	ns
Total peritonitis Episodes (n)	198	445	574	-
Male (%)	45.4	55.4	55.6	ns
DM (*n* and %)	34.4	25.9	22.9	0.01
APD (% at first peritonitis)	40.4	41.0	56.3	0.03
Mean age at start PD (yrs ± SD)	59.3 (15.4)	58.0 (14.6)	52.1 (15.8)	0.000
Mean RRF at start PD (l/wk/1.73m^2 ± SD)	41.0 (37.9)	53.0 (40.6)	59.3 (43.6)	0.000
Mean BMI (kg/m^2 ± SD)	24.5 (4.6)	25.9 (5.0)	26.5 (4.9)	0.000
Mean PD exposure to 30 June 2011 (yrs ± SD)	2.58 (2.0)	3.19 (2.3)	3.6 (2.5)	0.02
PRD (%)				
Primary GN	17.8	17.4	19.1	
Interstitial nephropathies	18.4	23.6	31.2	
Multisystem disease	17.2	23.6	14.6	0.000
Diabetic nephropathy	28.2	17.9	18.1	
Unknown or other	18.4	17.4	17.1	
Organism (%)				
CNS	17.2	29.9	35.2	0.000
Gram Negative	13.1	9.0	7.7	0.008
SA	15.7	12.1	12.4	ns
MRSA	3.0	1.8	1.6	ns
Fungal	1.0	1.6	3.0	ns
Other	26.8	25.8	24.2	ns
Pseudomonas	3.0	0.9	1.6	ns
Culture Negative	26.3	21.6	17.6	0.02
Peritonitis Outcome (%)				
Cure	78.3	76.6	76.7	ns
Refractory	18.7	21.1	21.6	ns
Relapse	12.6	10.1	8.4	ns
Death	3.0	2.2	1.7	ns
Technique Failure	11.6	14.2	14.1	ns

Peritonitis-free Survival

Patients with lower albumin at the start of PD have a shorter peritonitis-free survival ($p<0.001$) shown in figure 27.

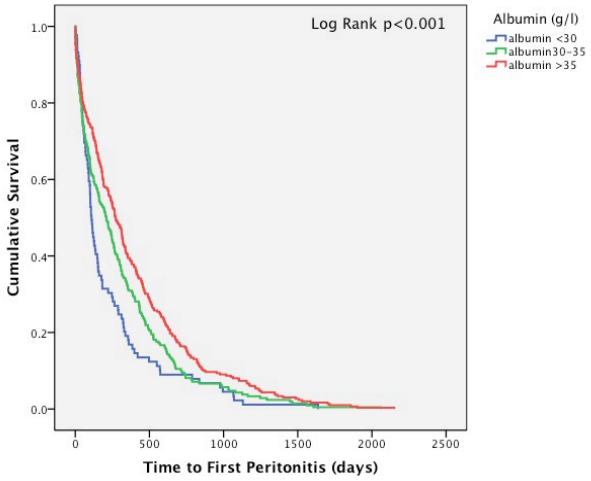


Figure 27. Kaplan Meier plot showing peritonitis-free survival according to serum albumin concentration at the start of PD.

5.4.3.6 RRF/Adequacy

Risk of Peritonitis

There is wide variation in RRF at the start of PD. There were no significant differences between anuric patients and those with <10 l/wk1.73m^2 therefore they have been grouped together, except with respect to peritonitis-free survival. The data were analysed by splitting into 6 groups (<10, 10-20, 20-30, 30-40, 40-50, >50 l/wk/1.73 m^2), but outcomes for renal clearances <10 l/wk/1.73m^2 were different from other categories, so the analysis thereafter compared RRF <10 versus ≥10 l/wk/1.73m^2. For 289 patients we do not have an adequacy measurement within the first 6 months.

Patients with no RRF measurement have lower PD exposure than the others and fewer experienced peritonitis (table 13). A larger proportion of patients with a renal clearance <10 l/wk/1.73m^2 developed peritonitis than those with renal clearance >10 l/wk/1.73m^2.

Those with clearance <10 l/wk/1.73m^2 are less likely to be cured, more likely to have refractory peritonitis and more likely to die from peritonitis than those with >10 l/wk/1.73m^2 RRF. However, those with RRF <10 l/wk/1.73m^2 are less likely to be male, have lower albumin and BMI.

Table 13. Comparison between patients with residual renal function (RRF) <10 and >10 l/wk/1.73m^2 and those for whom we do not have an adequacy measurement.

Variable	RRF <10 l/wk/1.73m^2	RRF ≥ 10 l/wk/1.73m^2	*RRF unknown*	*Analysis 1 P value$^\alpha$*	*Analysis 2 P value$^\alpha$*
Number of patients	117	918	289	-	-
Peritonitis experienced n (%)	81 (69.2)	488 (53.2)	99 (34.2)	0.000	0.001
Peritonitis episodes (n)	166	1014	138	-	-
% Male	44.4	56.8	51.9	0.02	0.008
% DM	21.4	24.1	32.2	0.03	ns
Mean age§ (yrs ± SD)	57.0 (16.1)	54.1 (15.5)	56.4 (16.3)	0.03	ns
Mean Albumin§ (g/l ± SD)	34.0 (6.5)	35.5 (5.1)	35.3 (5.4)	0.03	0.008
Mean BMI§ (kg/m^2 ± SD)	25.3 (5.0)	26.3 (4.9)	24.7 (4.0)	0.01	0.05
Median PD Exposure (days + IQR)*	480.0 (263- 857)	794.0 (423- 1228)	131.0 (47 - 332)	0.000	0.000
PRD (n)					
Primary GN	17.1	19.0	14.5		
Interstitial Nephropathy	22.2	27.8	23.9		
Multisystem Disease	25.6	16.9	20.1	0.004	0.03
DN	12.0	19.4	26.6		
Unknown	23.1	17.0	14.9		
Peritonitis: organism (%)					
CNS	27.9	24.9	13.0	0.000	0.4
Gram negative	13.1	10.0	12.2	ns	ns
SA	12.3	13.9	16.3	ns	ns
MRSA	2.5	1.8	1.6	ns	ns
Fungal	1.6	1.1	6.5	ns	ns
Other	22.1	24.7	23.6	ns	ns
Pseudomonas	3.3	1.7	3.3	ns	ns
Culture negative	17.2	21.9	23.6	0.01	ns
Peritonitis: Outcome					
Cure	69.8	83.6	65.2	0.000	0.03
Refractory	21.6	12.7	18.7	0.000	0.000
Relapse	9.9	13.1	9.1	0.05	ns
Death	8.6	3.7	6.1	0.02	0.02
Technique Failure	24.7	25.6	38.4	0.001	ns

α Analysis 1 compares all 3 groups: RRF <10, RRF >10 l/wk/m^{2}and RRF unknown.
Analysis 2 compares only RRF <10 versus RRF>10 l/wk/m^2.
§ Measurement at start of PD.
* Median PD exposure and interquartile range from start of PD to end June 2011

Peritonitis-free Survival

The patients with no RRF measurement have a significantly shorter peritonitis-free survival than anuric patients, those with RRF <10 and >10 l/wk/1.73m^2 (median 58 days (42.5-73.5), 182.0 (34.8-329.2), 291.0 days (206.9-375.1) and 250.0 days (209.7-290.3) respectively, p<0.001). The significant difference is between the unknown RRF group compared to the other groups shown in figure 28 below.

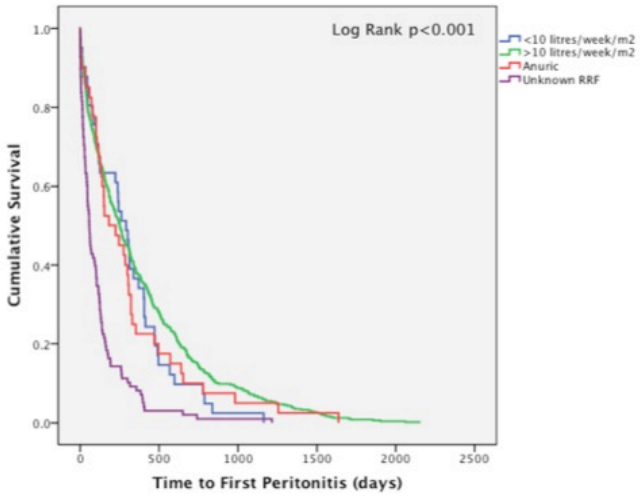


Figure 28. Peritonitis-free survival comparing differing degrees of RRF at the start of PD.

5.4.3.7 Deprivation Category

No association with SIMD score risk or peritonitis, time to first peritonitis, specific organisms or outcome of peritonitis.

5.4.4 Multivariate Analysis

5.4.4.1 Peritonitis-free survival

Factors associated with shorter peritonitis-free survival are: being on CAPD at the time of first peritonitis (p=0.001), age over 70 years at start of PD (p=0.008), being a female diabetic (p=0.05), hypoalbuminaemia (p=0.001), and RRF <10l/wk/1.73m^2 (p<0.001).

In the multivariate analysis the only predictors were serum albumin (HR 0.98 (0.96-0.99), p=0.005), and CAPD at first peritonitis (HR 1.40 (1.29-1.52 p=0.000). Therefore for every 1g/l increase in serum albumin, patients are 2% less likely to experience peritonitis.

5.4.4.2 Peritonitis vs no peritonitis

The factors found to be significant for experiencing peritonitis include, gender (males>female, p=0.04), mean age at start of PD (p=0.05), unit (p=0.007), and RRF (<10 versus >10 l/wk/m^2, p=0.001). These factors were analysed by logistic regression but as there are significant differences between units in mean BMI, and deprivation categories, these factors were also included in the logistic regression model. Unit remains the most significant predictor (HR 3.7, 1.8-7.8, p=0.000). Gender, with females less likely to get peritonitis, (HR 0.72, 0.56-0.93, p=0.01) and older age at the start of PD (HR 1.008, 1.000-1.02, p=0.04) are also predictors of peritonitis. When entered as a continuous variable, there is a trend toward lower RRF predicting higher risk of peritonitis (HR 0.997, 0.994-1.0, p=0.06), but when entered as a categorical variable <10 versus >10l/week/1.73m^2, RRF becomes a much stronger predictor of peritonitis, whereby patients with RRF <10l/week/1.73m^2 are more likely to get peritonitis (HR 1.96, 1.28-3.00, p=0.002).

5.5 Discussion

Despite our patient cohort undergoing PD in the era of flush-before-fill technology, over 50% are still experiencing peritonitis. This is a huge morbidity burden that carries significant resource implications for the health service. It is difficult to establish how Scotland compares to elsewhere, as most studies describe peritonitis rates in the prevalent PD population and do not refer to the proportion of patients experiencing peritonitis. Any treatment complication which will affect half of PD patients warrants further study. The various factors that may affect peritonitis risk may be split in to potentially modifiable, and non-modifiable factors. The modifiable factors largely relate to unit practice.

5.5.1 Potentially Modifiable Risk Factors

5.5.2 Unit

Our data shows that PD unit is an independent risk factor for peritonitis, even when PD duration, demographic factors, and other potential confounding factors are taken in to consideration. It is not clear is why two units have a greater proportion of patients experiencing peritonitis. There is evidence suggesting that units with a specialist PD interest, who generally have larger PD populations, have better peritonitis rates and outcomes but previous multi-centre Scottish and London data did not find significant differences between units (21, 22, 128).

Our data do not fully support the theory that larger "specialist" units have better rates and outcomes; unit 5 may be considered a specialist unit as it is the second largest in Scotland, yet it also has a higher peritonitis rate. The patient:nurse ratio in this unit is less favourable than other units (1:17) but other units with similar staffing levels have much lower peritonitis rates. There has been a high turnover of nursing staff in this PD unit, which raises the possibility that limited nursing experience may be contributing (129).

We cannot identify an obvious reason for unit 8's even higher peritonitis rate and of note it has a more favourable patient:nurse ratio (1:6) than most units. There were differences in antibiotic therapy prescribed between units with one unit not giving empirical gram negative cover despite recommendations to the contrary (16, 96). Our data demonstrate that this unit has lower cure rates, higher recurrence and higher technique failure rates in gram negative episodes of peritonitis than units that give ceftazidime. This unit has now adopted empiric gram negative cover for all episodes of peritonitis. Our data also suggest that ceftazidime offers advantages over oral ciprofloxacin therapy in terms of lower recurrence and technique failure rates. The numbers of cases are small for some comparisons which may explain why gentamicin and ciprofloxacin fail to show any significant benefit over no gram negative therapy. Recent evidence has raised questions about ciprofloxacin relating to bacterial resistance and poor outcome, albeit in the context of monotherapy (136).

More detailed comparisons between units in terms of staff experience, patient training and re-training methods were not possible retrospectively, but will be an area of ongoing study in the hope of modifying this risk factor for peritonitis.

5.5.3 CAPD versus APD

In our cohort APD is associated with a significantly lower peritonitis rate and significantly longer peritonitis-free survival (HR 1.40 (1.29-1.52 p=0.000). There may be an element of "era-effect" whereby more of the CAPD associated episodes were in the earlier half of the study period when more patients were on PD and arguably general PD technique may have improved toward the latter half of the study period.

Given the lack of consensus in previously published studies as to whether APD conveys a lower, equal or higher peritonitis risk than CAPD, one may argue that the modalities are equal, but it is the study methods that differ (22, 99, 115) (21, 120). Study methodology is crucial, especially when comparing one with another (137).

An example might be the study that spans a significant change in PD practice, such as the move to flush-before-fill technique. We feel our study has eliminated as many confounding factors as possible in as much as we have picked a study period in which technique has not changed perceptibly, we have included all incident PD patients, from all units, using data gathered prospectively over an 8 year period.

However, the conclusion from our data is still not clear cut; if APD carries a lower risk of peritonitis, one would expect that as APD usage increases, peritonitis rates should fall and this is not apparent in Scotland (138). However, units 4 and 10 who have had the highest usage of APD (94.0 and 81.8% respectively) also have the lowest proportion of patients experiencing peritonitis (41.1 and 34.9% respectively).

Similarly, the theory behind the potentially lower rate of peritonitis with APD is that there is less opportunity for touch contamination, as there are less connect-disconnect procedures. If this were the case, one might expect that there would be fewer CNS or SA related peritonitis episodes in APD patients, units with higher APD usage and indeed in the later years of the study where APD usage had increased. We have not observed this in our cohort. While the debate about whether APD offers a lower risk of peritonitis may continue, the other benefits of this modality are likely to ensure its dominant usage over CAPD.

5.5.4 SA Prevention Strategies

There is good evidence that SA nasal carriage carries an increased risk of SA peritonitis, and SA eradication with nasal mupirocin reduces exit site infections and peritonitis (22, 125, 126). Prophylactic mupirocin applied to the exit site has been shown to reduce SA peritonitis by up to 76% (139, 140).

The current (2011) ISPD position statement for reducing peritonitis recommend at least one method of SA prophylaxis (intra-nasal and/or to catheter exit site); and the evidence is greater for exit site prophylaxis in the PD population (98). There is the concern of developing mupirocin resistance, and which is the main reason our own, and most other Scottish units have not adopted mupirocin exit site prophylaxis as routine. Microbiologists and nephrologists in Scotland determine antimicrobial guidelines together.

Our data demonstrate that the unit not using SA nasal eradiation therapy has higher rates of SA peritonitis, SA peritonitis-related technique failure and a trend toward recurrent SA peritonitis. This is convincing evidence in our own population that SA nasal eradication therapy is effective. Our data suggests that units using exit site prophylaxis have higher rates of SA peritonitis and no difference in recurrence rates (13.1 versus 8.4% of peritonitis episodes, p=0.01). It is likely that these units started using exit site prophylaxis in response to a higher SA peritonitis rate, and possibly it is too early to observe any benefit. Given the limitation of our data, namely it is not patient specific and the units cannot tell us when exit site prophylaxis became routine, it is difficult to draw any meaningful conclusion. However, with convincing evidence from trials we are in discussion with Scottish PD units and microbiology departments to consider a nationwide policy for routine exit site prophylaxis with mupirocin (139).

Given the small numbers of SA peritonitis cases, to have sufficient patient numbers to establish if exit site prophylaxis is effective we would need to include all PD patients in Scotland, comparing to previous years of audit data as a control. There would also need to be close monitoring of mupirocin resistance. If there were a 75% reduction just in SA peritonitis rates in our population we would expect to see a corresponding improvement in our peritonitis rate from 1 every 19.9 months to 1 every 24.5 months, bringing our results more in line with North America where exit site prophylaxis is routine.

5.5.5 Non-Modifiable Risk Factors: Patient-related Features

5.5.5.1 Age

Old age has been associated with a higher peritonitis risk (0.52 vs 0.37 /patient-year for >70yrs and 40-70yrs respectively) but other studies have shown no difference (114, 115). Patients >70 years in our study are more likely to get peritonitis (for every year increase in age, HR 1.008, 1.000-1.02, p=0.04) and have shorter peritonitis-free survival (median 152.0 days vs 219.0 days for <70 years, p=0.008). This is likely to be multifactorial.

Older patients in our cohort have lower serum albumin concentrations, which appears to be the strongest predictor of peritonitis-free survival, but conversely are more likely to be on APD, which confers a reduced risk of peritonitis. Perhaps elderly patients are more likely to get peritonitis because they are more likely to be infirm or struggle to perform exchanges and have accidental contamination. Interestingly, French data examining the role of nurse-assisted PD for elderly patients found that patients with nurses assisting them were *more likely* to get peritonitis, and had shorter peritonitis free survival than patients or patients' family doing their exchanges (141). This would suggest that the increased risk in elderly is not immediately attributable to poor technique and the finding that patients > 70 years in our study are less likely to have CNS peritonitis supports this.

As with previous studies, our data show that elderly patients experience more gram negative peritonitis, reflecting the increased likelihood of underlying pathologies such as diverticular or other intestinal disease (114). In keeping with the higher rate of less curable organisms, the >70 year olds are less likely to be cured and more likely to die from peritonitis. However, on multivariate analysis, age is not a predictor of peritonitis.

5.5.5.2 PRD

We could find no relationship between primary renal diagnosis and risk of peritonitis, risk of specific organisms, or outcome of peritonitis, with the exception of diabetes mellitus. For example, in theory patients with adult polycystic kidney disease may be more likely to experience gram negative peritonitis secondary to cyst infection or rupture, but this was not suggested by our data analysis.

5.5.5.3 Diabetes Mellitus

Previous studies have shown shorter peritonitis-free survival in diabetics (119, 124). Our cohort shows a trend toward shorter peritonitis-free survival in diabetics versus non-diabetics but this is only significant in females (median 138.0 days (87.4-188.6) versus 224.0 days (155.9-292.4) p=0.05). We did not find that diabetic females have a higher rate of peritonitis per se, as has been suggested previously (115).

The shorter peritonitis-free survival is confounded by the lower serum albumin levels in these patients. Indeed, using Cox regression analysis for peritonitis-free survival, DM is not an independent predictor of shorter peritonitis-free survival, even when females are analysed separately, whereas serum albumin is (HR 0.98 (0.96-0.99) p=0.009).

In contrast to our own findings, Chow et al found that diabetics were more likely to have gram negative peritonitis (119). In our cohort, a higher proportion of diabetics suffer SA peritonitis (p=0.006) and diabetics have significantly higher rate of peritonitis recurrence (not specifically SA recurrence) (p= 0.0001). Whilst exit site prophylaxis with antibiotic preparations is not routine practice in Scottish renal units, there would be a very strong argument for at least targeting its use to the diabetic PD patients.

5.5.5.4 BMI

Previous evidence suggested that obesity (BMI >25) is associated with increased risk of exit site infections, peritonitis, reduced peritonitis-free survival, more frequent refractory outcome and more peritonitis recurrences than patients with normal BMI (116-118). There is also evidence that underweight individuals (BMI<20) may have a lower risk of peritonitis than patients in the normal weight group (116). Although we have no information about episodes of exit site infections in our population, we could not find any relationship between BMI, risk of peritonitis, causative organisms or outcome of peritonitis. Our study may be too small to detect a difference, given that McDonald's study using ANZDATA database included 10,709 patients.

5.5.5.5 Psychosocial Factors

There are no published data describing the effect of socioeconomic status or deprivation category on risk of peritonitis or poor outcome from peritonitis in Western PD populations. Scotland has some of the most deprived communities in Europe as well as more affluent areas. Our study includes patients from socioeconomic groups as there is no alternative provision for renal replacement therapy outwith the National Health Service. Despite a large study population and an even spread of patients across deprivation categories, we found no association between deprivation category, risk or outcome of peritonitis.

We had no information regarding patients' psychological well-being but acknowledge that depression is common in patients with end-stage renal disease and has been linked to increased risk of peritonitis in PD patients (134, 135). Whether screening for, and treating depression would impact upon peritonitis rates is yet to be established.

5.5.5.6 Serum Albumin or Malnutrition

Patients in our cohort with lower serum albumin measurements are significantly more likely to be diabetic, have a lower mean BMI, and lower RRF. However, Cox proportion hazards analysis reveals serum albumin concentration at the start of PD to be an independent predictor of peritonitis (HR 0.98 (0.96-0.99), p=0.005); for every 1g/l increase in serum albumin, patients are 2% less likely to experience peritonitis. This finding is in keeping with smaller studies' results, whereby malnutrition is associated with a higher peritonitis rate, and shorter peritonitis-free survival (119, 121, 123, 124, 142).

Hypoalbuminaemia is established as a surrogate measure of poor health; associated with increased risk of death and morbidity in the general population and the HD population (143). In a study of dialysis patients, a 1 g/dL decrease in serum albumin was associated with an increased mortality risk of 47% in HD patients and 38% in PD patients (144). In the PD population few studies have focused on serum albumin and peritonitis risk, but several have shown low serum albumin to be an independent predictor of morbidity, mortality and reduced PD technique survival (145-147).

Diabetics in our population are more likely to have hypoalbuminaemia at the start of PD (p=0.001). This may reflect the fact that patients with diabetic nephropathy often have significant urinary protein losses. Add to this the additional potential for peritoneal protein losses and it becomes difficult to untangle what a low serum albumin reflects; poor nutrition or high losses. Would a patient with hypoalbuminaemia from heavy proteinuria actually have more to gain by losing RRF and thus potentially improving serum albumin, than from preserving their RRF at all costs? Or is the albumin concentration irrelevant, but rather what it signifies; general ill health. There is a need for detailed studies examining the interrelationship between these factors and their impact on patient outcomes.

In the meantime, it is difficult to discuss modifying a risk factor, when one cannot clearly state what the risk factor is; hypoalbuminaemia is likely to be the surrogate marker for several risk factors or for poorer health in general.

5.5.5.7 Residual Renal Function

There are very little data published regarding RRF and risk of peritonitis, particularly in adults. RRF has been shown to be an independent risk factor for peritonitis (for every 1ml/min/1.73m^2 increase, HR 0.81, $p<0.01$) and is associated with shorter peritonitis-free survival (124). A paediatric study, also suggests that reduced RRF is an independent risk factor for peritonitis, but they do not quantify the risk (127).

The patients with no RRF measurement have a significantly shorter peritonitis-free survival than anuric patients, those with RRF <10 and >10 l/week/1.73m^2 (median 58 days (42.5-73.5), 182.0 (34.8-329.2), 291.0 days (206.9-375.1) and 250.0 days (209.7-290.3) respectively, $p<0.001$). The patients from our cohort with no RRF measurement also have a lower PD exposure than the others and fewer have experienced peritonitis. Shorter time on PD for some patients will mean fewer opportunities to develop peritonitis, but for others is an indication that the technique failed early, frequently because of peritonitis. Thus although smaller proportion of the "unknown RRF" group experienced peritonitis, their mean peritonitis-free survival is significantly shorter as it is skewed by the patients who developed peritonitis early on and had to stop PD. This group are therefore self-selected and it is not unexpected that they have a fewer cures, more deaths and a larger proportion of technique failures attributable to peritonitis; this is the reason many have not continued PD long enough to have an adequacy check.

We have shown that a significantly larger proportion of patients with a RRF <10 developed peritonitis than those with RRF >10 l/wk/1.73m^2 (p=0.001). Those with RRF <10 l/week/1.73m^2 are less likely to be cured (p=0.03), but are also more likely to die (p=0.02) from peritonitis. The higher mortality may relate to the nutritional status of patients with lower RRF, as described below. However, those with RRF <10 l/wk/1.73m^2 are also significantly less likely to be male, have a lower albumin and lower BMI than the others. Despite this, on multivariate analysis RRF remains an independent risk factor for peritonitis.

It has been shown that once CKD patients' creatinine clearance falls below 14 ml/min/m^2, they are at greater risk of malnutrition. It may follow that as RRF falls, patients are more likely to become malnourished. If this were the case then perhaps lower RRF is a surrogate marker of malnutrition in our cohort, which is supported by the significantly lower BMI and albumin in those with lowest RRF.

Once PD commences RRF tends to decline, which raised the question as to whether nutritional status also continues to fall. This hypothesis was tested in a small prospective study (n=46) including measures of subjective global assessment, dietary protein intake and well as serum albumin. In contrast to what the authors were expecting, despite rapid fall in RRF, the prevalence of malnutrition fell from 62.5% at start of PD to 18.8% within a year (p<0.05) (148).

Another study (n=23) compared patients with DM to non-diabetics and found that rather than showing progressive improvement like non-diabetics, those with DM showed no change or a deterioration in several nutritional parameters in the first year of PD treatment (p<0.05) (149).

The interrelationship between RRF, serum albumin, DM, nutritional status, BMI, and PD related protein loss is complex and difficult to correct for in any statistical analysis. From our data RRF would appear to be a significant risk factor when renal clearance falls below approximately 10 l/wk/1.73m^2. Given that RRF has been shown to influence patient and technique survival, efforts should be made to preserve RRF regardless of whether it impacts upon risk of peritonitis (24, 150-153) .

Whether PD adequacy per se, or the delivered peritoneal clearance confers any benefit or risk is not clear and we did not have enough information to analyse this meaningfully.

Does it all come back to serum albumin and nutrition?

Leaving PD unit aside, serum albumin, diabetes mellitus, lower RRF and age are all risk factors for peritonitis or specific outcomes of peritonitis. On multivariate analysis albumin is the most significant. The observation that diabetics have a higher risk, which is confounded by low serum albumin, and the study evidence that diabetics' nutritional status does not improve during the first year of PD raised the possibility that low albumin, or nutritional status may actually be the reason for diabetics' higher risk (149). Similarly, lower levels of RRF are associated with lower serum albumin and poorer nutrition. The older patients in our study also had a lower serum albumin, particularly the older females. Therefore the major risk factors in our population can all potentially be related to a low serum albumin. In the absence of other measurements of nutritional status, it is not possible to say that malnutrition is the problem, simply that hypoalbuminaemia is associated with higher risk. How one may modify that risk is difficult to see until we have more detailed studies.

5.6 Conclusions

As long as PD peritonitis remains a significant cause of morbidity, and the leading cause of PD technique failure, efforts should be made to identify and modify possible risk factors. Our study has demonstrated that the PD unit, being on CAPD, low serum albumin, lower RRF, diabetes mellitus in females and patient age all confer a higher risk of peritonitis or shorter peritonitis-free survival. More detailed study is required to establish possible reasons why certain PD units are associated with higher risk, in the hope of adopting good practices and modifying this risk factor. Despite the possibility of an era effect, our data clearly suggest APD carries a lower risk of peritonitis, but given that the vast majority of PD patients now use APD with no improvement on peritonitis rates, there is little scope to modify this risk factor any further. Hypoalbuminaemia is one of the strongest independent risk factors in our analysis, and may simply be a surrogate marker of patient ill health.

While the patient-related risk factors are not immediately modifiable, we would suggest that patients with these risk factors be the focus of any preventative strategies for PD peritonitis.

Chapter 6

Peritoneal Dialysis Adequacy Testing; bringing the Focus to Residual Renal Function

6. Peritoneal dialysis adequacy testing; bringing the focus to residual renal function.

6.1 Introduction

Inadequate PD is a major cause of PD technique failure but its impact on patient morbidity and mortality is poorly defined. However, the crucial importance of residual renal function (RRF) to technique and patient survival is apparent, and arguably maintaining residual renal function should be the focus when managing PD patients.

6.1.1 Definition of PD adequacy

Adequate peritoneal dialysis (PD) is difficult to define and its relationship to patient outcome is controversial (154). Adequate PD may be defined as the absence of uraemic symptoms, appropriate fluid balance and acceptable serum biochemistry. However, the major guidelines all include measurement of small solute clearance with recommended minimum targets as part of PD adequacy assessment (155-159). All guidelines recommend a lower acceptable limit for weekly small solute clearance but no upper target.

6.1.2 Impact of PD adequacy on patient outcomes

There is clear evidence that RRF impacts upon patient outcomes but randomised controlled trials examining the effect of increasing peritoneal clearance have not shown a survival benefit (24, 151, 155, 158). However, there is evidence that a lower level of achieved PD clearance has adverse effects whereby anuric patients with a Kt/V_{urea} of <1.5 or creatinine clearance <40 l/wk/1.73m^2 have an increased risk of death (150). A recent study from the Australian and New Zealand Registry (n=2434) found a U-shaped relationship with peritoneal Kt/V whereby overall survival is optimal in those with peritoneal Kt/V 1.7-2.0 but significantly worse when peritoneal Kt/V is <1.45 or >2.0 independent of RRF (9).

However, this study also found that lower RRF was an independent predictor of death, with anuric patients having poor survival rates despite achieving higher peritoneal Kt/V and the authors conclude that RRF is quantitatively a more important determinant of survival than peritoneal clearance. While the debate about increasing peritoneal clearance may go on, current literature agrees that clinicians should aim for a minimum total PD clearance (combined renal and peritoneal clearances) and should strive to maintain RRF in the hope of prolonging PD technique success and improving patient outcomes.

6.1.3 Targets for PD Adequacy

Guidelines have suggested measuring renal and peritoneal clearance every 4-6 months but PD adequacy tests are time-consuming and cumbersome to measure. Minimising the workload and costs involved is desirable. Previous work from Traynor *et al* on behalf of the Scottish Renal Registry (SRR) assessed formulae for estimating total PD adequacy without the need for formal adequacy tests (160). They concluded that prediction formulae were not accurate enough to reliably detect underdialysis in PD patients.

6.1.4 Study Hypothesis

Our belief is that measuring renal clearance alone may be sufficient in a large proportion of PD patients. Clinical experience and data from large studies suggest that typical PD (CAPD or APD) prescriptions provide around 40 l/wk/1.73 m^2 of peritoneal creatinine clearance. It should follow that a patient would require a minimum of 20 l/wk/1.73 m^2 of residual renal clearance to achieve a total clearance around 60 l/wk/1.73 m^2. Therefore, renal clearance could potentially be sufficient to predict adequate dialysis without the need for additional PD clearance measurement on every occasion. This would have the added benefit of bringing the main focus of PD adequacy measurement to residual renal function and methods of preserving it.

Since completing this project, the most recent Canadian Society of Nephrology (CSN) Guidelines suggest that routine measurement of peritoneal transport status or peritoneal clearance is *not* required in patients achieving a peritoneal Kt/V of 1.7 (peritoneal creatinine clearance >50l/week/1.73m^2) unless there is a change in the patient's clinical or biochemical status and but recommend measuring renal clearance every 3-6 months (161). The authors base these recommendations on opinion, in the absence of published evidence, highlighting the need for data to support this practice.

6.2 Study Aim

The aim of this study was to assess if a renal clearance measurement alone could be used to identify patients who reliably achieve current PD adequacy targets without the need for routine PD clearance measurement.

6.3 Materials and Methods

6.3.1 Dataset

Since 1999 all 10 adult renal units in Scotland aim to measure PD adequacy for all PD patients every 6 months, repeating tests more frequently if indicated. This data is gathered prospectively and reported every 6 months to the SRR in handwritten paper format. Results from 01 January 1999 – 31 December 2007 were analysed for this study. The data include measurement of a 24 hour urine collection to calculate a weekly renal clearance (mean of urea and creatinine in litres/week) and total weekly PD creatinine clearance (corrected for glucose concentration) both corrected to body surface area (BSA) 1.73m^2 (l/wk/1.73 m^2). Units used either the batch or multiple-aliquot method to sample the dialysate; these methods have been shown to produce comparable results (162). Incomplete data and data uncorrected for glucose concentration or BSA were not included.

For patients with serial results, the most recent adequacy data was used to ensure that there was a proportion of patients with low or no residual renal clearance. The data from all units were pooled, sorted alphabetically by patient name, and the results from every fifth patient were separated to split the group in two to make a larger "test group" and a smaller "validation group". The larger group was used for data analysis to determine potential "cut-offs" for renal clearance, and the smaller group was used to test if the adequacy of PD could be assessed reliably using these cut-offs. The renal, peritoneal and total clearances were analysed. This allowed identification of potential thresholds for renal clearance that would predict adequate total clearance and further analysis was focussed on this range of renal clearances.

The sensitivity, specificity, positive and negative predictive values for predicting various targets of total clearance (combined renal and PD clearances) relating to specific renal clearance thresholds were calculated. Receiver operator curves (ROC) were plotted for target total clearances of 50, 60 and 70 l/wk/1.73 m^2 to identify optimum minimum renal clearance values for predicting adequate total clearance. The renal clearance levels that performed best were then used to analyse the "validation group" data (n=332).

6.5 Results

6.5.1 Dataset

Our dataset comprised 5492 individual adequacy results from 1676 prevalent patients. Data from 1664 individual patients met the criteria for analysis of which 1332 were used for the "theory group" and 332 were used as a "validation group". Test results from 12 patients were omitted because they were incomplete and there was no other result to substitute. The median age was 57 (IQR 34 – 68 years) and 50.1% were male. The Scottish PD population is over 95% Caucasian. The average body mass index (BMI) was 26.1 kg/m^2.

6.5.2 PD Clearance details

Of the 1664 patients included in analysis, 90.1% achieved a total clearance (renal and PD clearance combined) ≥ 50 l/wk/1.73 m^2, 72.7% achieved a total clearance ≥ 60 l/wk/1.73 m^2 and 53.1% achieved a total clearance ≥ 70 l/wk/1.73 m^2. The average total clearance was 79.3 (median 71.3, IQR 58.6 – 91.4) l/wk/1.73 m^2. The average renal clearance was 32.2 (median 21.5, IQR 3.2 – 49.5) l/wk/1.73 m^2 and 20.1% of patients were anuric. The average peritoneal clearance was 47.2 (median 46.7, IQR 37.4 - 56.4) l/wk/1.73 m^2.

When sorted and divided by specific cut-offs for renal clearance, the proportion of patients achieving ≥ 50, ≥60 and ≥ 70 l/wk/1.73 m^2 total clearance is shown in Table 14. As expected there is a clear relationship between residual renal clearance and likelihood of achieving adequate total clearance.

Table 14. Absolute numbers and proportion of patients achieving the total target creatinine clearances within each range of renal clearances

Renal Clearance	TC§ < 50 l/wk	TC ≥ 50 l/wk	Cumulative TC ≥ 50 l/wk		TC < 60 l/wk	TC ≥ 60 l/wk	Cumulative TC ≥ 60 l/wk		TC < 70 l/wk	TC ≥ 70 l/wk	Cumulative TC ≥ 70 l/wk	
l/wk	n	n*	n	%	n	n*	n	%	n	n*	n	%
0	59	201	1202	90.2	149	111	969	72.7	214	46	707	53.1
≥0 – 4.9	25	79	1001	93.4	67	37	858	80.0	94	10	661	61.7
≥5 – 9.9	19	83	922	95.2	54	48	821	84.8	84	18	651	67.3
≥10 – 14.9	12	81	839	96.9	36	57	773	89.3	67	26	633	73.1
≥15 – 19.9	8	63	758	98.1	25	46	716	92.6	46	25	607	78.5
≥20 – 24.9	6	83	695	99.0	18	71	670	95.4	50	39	582	82.9
≥25 – 29.9	1	58	612	99.8	7	52	599	97.7	26	33	543	88.6
≥30 – 34.9	0	64	554	100.0	4	60	547	98.7	17	47	510	92.1
≥35 – 39.9	0	59	490	100.0	3	56	487	99.4	12	47	463	94.5
≥40 – 44.9	0	47	431	100.0	0	47	431	100.0	11	36	416	96.5
≥45 – 49.9	0	45	384	100.0	0	45	384	100.0	4	41	380	99.0
≥50 – 54.9	0	42	339	100.0	0	42	339	100.0	0	42	339	100.0
≥55 – 59.9	0	39	297	100.0	0	39	297	100.0	0	39	297	100.0
≥60	0	258	258	100.0	0	258	258	100.0	0	258	258	100.0
Total	130	1202		90.2	363	969		72.7	625	707		53.1

§ TC = total PD clearance ie combined peritoneal and renal clearance. "n" refers to the number of patients within the range of renal clearance specified who achieve the specified target total clearance e.g. renal clearance ≥ 20 to 24.9 l/week, 58 of 59 patients achieve total clearance > 50 l/week and ≥ 25 to 29.9 l/week, all 64 patients achieve total clearance > 50 l/week.

It is apparent that the vast majority of patients (> 90%), even if anuric, achieve total weekly clearances > 50 litres/week. If the target total clearance is >70 l/wk/1.73 m^2 then patients require approximately 30 l/wk/1.73 m^2 or more renal clearance for > 90% to achieve the target.

The data are shown as ROC plots (figure 29) for target total target clearances of 50, 60 and 70 l/wk/1.73 m^2. Depending on which target total clearance is chosen, renal clearances between 20 – 40 l/wk/1.73 m^2 appear to be the most discriminatory or the lower threshold for predicting adequate total clearance.

Figure 29. Receiver operator curves for target total clearances of 50, 60, and 70 l/wk/1.73 m^2 according to different thresholds for renal clearances.

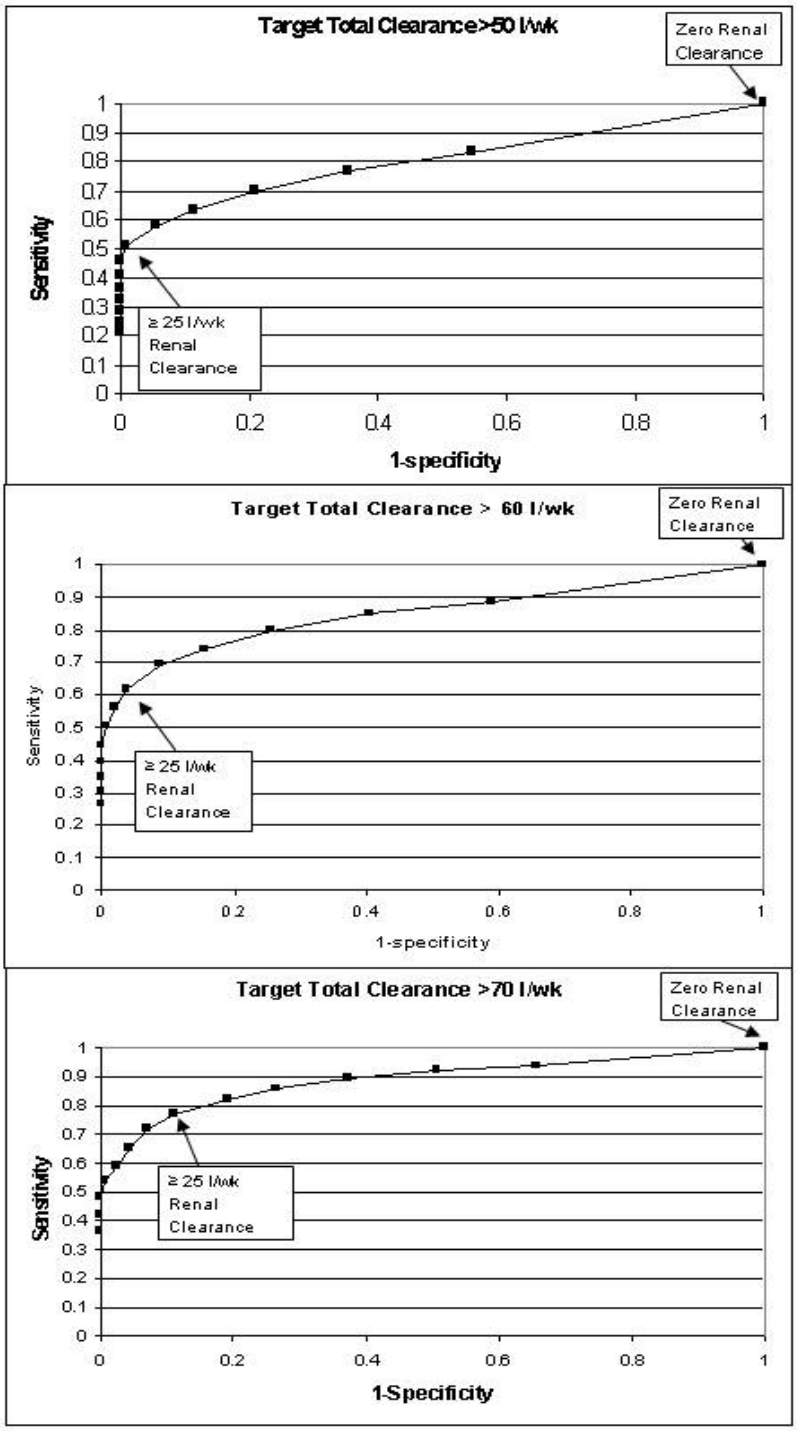


Table 15 shows the sensitivity, specificity, prevalence, positive predictive value (PPV) and negative predictive value (NPV) of using renal clearances of ≥20, ≥25, ≥30, ≥ 35, ≥40 l/wk/1.73 m^2 renal clearance to predict total clearances of >50, >60, and >70 l/wk/1.73 m^2.

Table 15. Sensitivity, specificity, prevalence, positive and negative predictive values for predicting total clearances of >50, >60 and >70 l/wk/1.73m2 according to specific cut-offs for renal clearance.

RC	Target Total Clearance														
	50 litres/week					60 litres/week					70 litres/week				
(l/wk)	Sens (%)	Spec (%)	Prev (%)	PPV	N PV	Sens (%)	Spec (%)	Prev (%)	PPV	NPV	Sens (%)	Spec (%)	Prev (%)	PPV	NPV
≥ **40**	35.9	100	32.4	1	0.76	44.5	100	32.4	1.00	0.79	58.8	97.6	32.4	0.92	0.83
≥ **35**	40.8	100	36.8	1	0.74	50.3	99.2	36.8	0.97	0.77	65.5	95.7	36.8	0.90	0.83
≥ **30**	46.1	100	41.6	1	0.72	56.4	98.1	41.6	0.95	0.76	72.1	93.0	41.6	0.88	0.82
≥ **25**	50.9	99.2	46.1	0.98	0.70	61.8	96.1	46.1	0.93	0.75	76.8	88.8	46.1	0.85	0.82
≥ **20**	57.8	94.6	52.7	0.92	0.67	69.1	91.2	52.7	0.90	0.73	82.3	80.8	52.7	0.83	0.80

RC = renal clearance, Sens = sensitivity, spec = specificity, prev = prevalence, PPV = positive predictive value, NPV= negative predicitive value.

As the aim of the study is to determine the minimum renal clearance that will predict adequate total clearance, a high specificity is more important than a high sensitivity; we do not want to miss patients with inadequate total clearance (false negatives). The balance is between maintaining specificity and aiming for maximal practical benefit in terms of reducing the number of PD clearance measurements to a minimum.

From the test group data, the lower threshold of renal clearance for predicting overall adequacy whilst maintaining acceptable specificity and optimum practical benefit appears to be in the range of 20-40 l/wk/1.73 m^2. We used the 332 patients in our "validation group" who were not part of the initial analysis to test different thresholds within this range of renal clearances to see if the same degree of specificity was maintained. The results are shown in table 16. The results are comparable to those found in the analysis of the test population, with particularly high specificity for renal clearances 20-40 l/wk/1.73 m^2.

Table 16. Data from the "validation group" (n=332) showing patients achieving target total clearances of 50, 60 and 70 l/wk/m^2 for renal clearance 20 - 40 l/wk/1.73m2.

Renal Clearance		Total Clearance					
Cut-Off		≥ 50 l/wk		≥ 60 l/wk		≥ 70 l/wk	
(l/wk)	n	n	%	n	%	n	%
≥ 40	100	100	100.0	100	100.0	100	100.0
< 40	232	198	85.3	129	55.6	61	26.3
≥ 35	111	111	100.0	111	100.0	108	97.3
< 35	221	187	84.6	118	53.4	53	24.0
≥ 30	126	126	100.0	125	99.2	116	92.1
< 30	206	172	83.5	104	50.5	45	21.8
≥ 25	147	147	100.0	146	99.3	126	85.7
< 25	185	151	81.6	83	44.9	35	18.9
≥ 20	161	160	99.4	156	96.9	133	82.6
< 20	171	138	80.7	73	96.9	28	16.4

6.6 Discussion

As long as the definition of adequate PD and its relationship to patient outcomes remains uncertain, clinicians and nurses must make their own decisions regarding small solute clearance targets for their patients. Guidelines recommend minimum lower thresholds for small solute clearances but there is an expert opinion that we should aim above these targets in order to reliably meet them.

Central to this is the concept of adequate versus optimum dialysis. Achieving optimum dialysis does not simply refer to adequate solute clearance, but the complex balance of patient symptoms, serum biochemistry, fluid balance and ultrafiltration, cardiovascular risk factors and patient well-being. The relative balance of these factors will be patient-specific, and it is difficult to create an all-inclusive guideline appropriate to all patients within the confines of the current evidence base. With this is mind, our study focuses on one aspect of assessing adequate or optimum dialysis for PD patients in an attempt to answer a practical question. We are not attempting to define what appropriate targets should be or suggesting that solute clearance alone be the focus of patient management.

The target Kt/V_{urea} or creatinine clearance that should be aimed for is unclear. The ADEMEX and Hong Kong studies (randomised controlled trials) found no survival benefit when peritoneal Kt/V_{urea} was increased above 1.7 or peritoneal creatinine clearance was >46 litres/wk/m^2 (151, 155). The NECOSADD study did find an increased mortality in anuric PD patients if the achieved adequacy was Kt/V_{urea} <1.5 or creatinine clearance <40 l/week (150). However, survival is not the only relevant patient outcome. For example, more patients in the control group of ADEMEX dropped out from PD as a result of uraemic symptoms and those with a Kt/V_{urea} < 1.7 in the Hong Kong study were also more likely to drop out and had more significant anaemia.

Most guidelines suggest a target total clearance of Kt/V_{urea} should be >1.7 and/or creatinine clearance >45 litres/wk/1.73m^2 (KDOQI, ISPD, European Best Practice Guidelines) (156, 157, 163) but Scottish units aim for the UK Renal Association target of total creatinine clearance >50 litres/wk/m^2 (159). We chose >50 litres/wk/1.73m^2 as our lower limit for analysis to allow a greater margin of error for units aiming for lower targets. We also analysed the data for 3 different target total clearances (50, 60 and 70 litres/wk/1.73m^2) to allow for future target changes, or for clinicians aiming for higher targets.

There are other considerations which may affect what targets clinicians aim for. If patients have uraemic symptoms, suboptimal biochemistry or ongoing unexplained anaemia it is reasonable to try to increase the total achieved small solute clearance. Transporter status has been shown to affect outcome, with low and low-average transporters having better survival than high or high-average transporters, even when adjusted for delivered dialysis dose (164). It is more difficult for low transporters to achieve the higher PD clearance targets and KDOQI guidelines suggest that in these patients a lower creatinine clearance may be acceptable without jeopardising patient outcome (157).

In our cohort it is interesting to note that >90% of all patients achieve a total clearance >50 litres/wk/1.73m^2. Of the 300 anuric patients, 20.7% fail to achieve total clearances >50 litres/wk/1.73m^2, and only 12.0% fail to achieve total clearance >45 litres/wk/1.73m^2. However, there may be a degree of bias in the data whereby anuric patients who were struggling (e.g. uraemic symptoms, suboptimal electrolyte balance) are less likely to have adequate total clearance and are more likely to have discontinued PD whereas the anuric patients who achieve adequate peritoneal clearances may be over-represented in the dataset.

Given the lack of consensus regarding the minimum PD dose for adequate dialysis, it would be inappropriate to give recommendations about the frequency of performing peritoneal adequacy tests or the minimum target small solute clearance. We envisage that our data may be used by clinicians to decide whether routine collection and analysis of PD effluent is required on every occasion when assessing PD adequacy using current guidelines, particularly for patients with significant RRF. This is likely to be determined by what is the minimum target small solute clearance aimed for by individual clinicians and what they deem is an acceptable number of inadequate total clearances (false negatives) that may be missed by picking a specific renal clearance cut-off.

From a practical perspective, a reduction in the number of PD effluent collections and laboratory analysis could reduce significantly the patient burden for monitoring of treatment adequacy, staff workload and costs. For example in this study, if we selected ≥20 litres/wk/1.73m^2 as the renal clearance above which we decide not to check peritoneal clearance, we would miss 7 patients with total clearances <50 litres/wk/1.73m^2 but if we chose a renal clearance ≥25 litres/wk/1.73m^2 we would only miss 1 patient with a total clearance <50 litres/wk/m^2. By selecting ≥30 litres/wk/1.73m^2 we would not miss any.

As shown in table 2, >46% of the PD population in our analysis had renal clearances ≥30 litres/wk/1.73m^2 which would mean if this were our threshold for not checking PD clearance, there would be almost 50% fewer PD clearance collections, a substantial reduction in cost and workload, whilst still maintaining a specificity of 100%.

RRF clearly relates to PD technique and patient survival (24). In one study the authors showed that each 1ml/min increase in renal creatinine clearance, but not peritoneal clearance, was associated with a 12% reduction in the odds ratio for death, highlighting that peritoneal clearance is inferior to the equivalent renal clearance (152). Prioritising measurement of the renal contribution to PD adequacy could help shift nurses' and clinicians' focus to the crucial target of preserving RRF.

The recent CSN guidelines support this practice, and this signals a shift in practice to target investigations rather than performing them routinely with no measurable benefit to the patient. The current K/DOQI and CSN guidelines specifically recommend measurement of renal clearance every 2-4 months, but this is not currently performed routinely in Scotland (157, 161). Following this practice would give ample opportunity to identify patients with declining RRF who could then have their peritoneal clearance checked and PD prescription modified as necessary. It would also highlight the importance of RRF to the patient who would be shouldering the main burden of the extra measurements.

Recent observational evidence from ANZDATA suggests that increments in the achieved peritoneal clearance may also have a positive impact upon patient survival independent of RRF, which would serve as a counter argument in support of regular peritoneal clearance measurements and aiming for optimal peritoneal clearance even in those with significant RRF (150).

However, this observational data is not supported by the evidence from the ADEMEX and Hong Kong randomised studies. Therefore, we would argue that the practical benefit of reducing the frequency of peritoneal clearance measurements outweighs the benefits of knowing the exact peritoneal clearance in patients who have sufficient RRF to meet the target for total small solute clearance per week and are otherwise doing well. This may well change if randomised controlled studies find evidence to convince the PD community that modification of PD regimens will benefit PD patients.

6.7 Limitations

Measurement of small solute clearance remains a major component of the clinical and laboratory assessment of the adequacy of PD. However it is not an exact science and measurement of small solute total (peritoneal and renal) weekly clearances is liable to intra-patient variation and inaccuracies, particularly outside the strict methodology of a clinical study. Our data represent adequacy results as measured in a real-life clinical setting, and will inevitably, and unavoidably, include inaccuracies such as incomplete urine or peritoneal effluent collections.

6.8 Conclusion

Measurement of weekly residual renal clearance can be used to predict if total small solute clearance is likely to be adequate in PD patients and so allow peritoneal clearance measurements to be performed less often or postponed in such patients. This study emphasises the high utility of regular measurements of renal clearance, highlights the importance of preserving residual renal function in PD patients and provides a safe alternative approach to the burden and cost of performing regular peritoneal clearance measurements in all PD patients.

Chapter 7

Encapsulating Peritoneal Sclerosis in the New Millennium: Clinical Characteristics and Outcomes in an Incident PD Cohort.

7. Encapsulating peritoneal sclerosis in the new millennium: clinical characteristics and outcome in an incident PD cohort

7.1 Introduction

Encapsulating peritoneal sclerosis (EPS) is a devastating complication of peritoneal dialysis (PD), first described in 1980 (27). EPS is thought to result from chronic intra-abdominal inflammation which is multi-factorial in origin. Prolonged PD represents the most consistent "risk factor" identified to date (28-32). The clinical features of EPS have been described previously (28-33, 165). As shown in these studies, onset may occur on PD, but most cases become apparent after stopping PD, including after renal transplantation. Clinical, radiological and pathological criteria for EPS diagnosis were defined by the International Society for Peritoneal Dialysis (ISPD) in 2000 (43).

There is little evidence to guide management of EPS patients. In Japan, enterolysis (surgical division of adhesions) is recommended but there are few European reports on EPS surgery (166-171). The role of total parenteral nutrition (TPN) peri-operatively is considered vital, and specialist centres advocate TPN until adequate enteral nutrition can be re-established, even long-term (172, 173). There are no randomised controlled trials of medical therapy for EPS. Based upon small case series and one larger retrospective analysis, oral corticosteroid with or without Tamoxifen show the most encouraging results (29, 33, 174, 175). Animal studies examining more targeted therapies such as blocking the pro-fibrotic transforming growth factor β (TGF-β) signalling have shown some encouraging results (176).

There are no reliable biochemical or radiological screening tests to identify patients at risk of, or in the early stages of EPS (177, 178). Studies are ongoing looking at potential substances in the PD effluent that may herald the onset of EPS (179).

Survival is poor for patients diagnosed with EPS. The impact of the various treatments is difficult to measure, as no treatment has been subjected to a clinical trial. Retrospective studies have suggested that patients treated, whether it be with Tamoxifen, steroids, or other immunosuppressants, have superior survival compared to those not treated, but the data is not robust enough justify inclusion in relevant guidelines (174, 180).

7.2 Aim

The aim of this study was to characterise the EPS cases diagnosed in patients using PD for end stage renal failure (ESRF) in Scotland between 01 January 2000 and 31 December 2007 and identify potential risk factors for EPS development.

7.3 Methods

The 10 adult renal units in Scotland identified potential EPS cases diagnosed on or after 01 January 2000. The initial data search included all EPS cases diagnosed in the study period regardless of the date they commenced PD. After 30/12/2007 we only collected data for patients who had commenced PD after 1st January 2000-31st December 2007 (i.e from the incident PD cohort). The cohort of incident adult patients who started PD between 1st January 2000 and 31st December 2007 in Scotland (n=1238) was identified from the Scottish Renal Registry (SRR) at the beginning of 2008. All cases have been used to describe the clinical presentation.

Only incident cases who started PD after 01 January 2000 are used for survival analysis and for comparisons with the incident PD population who did not develop EPS. For clarity we refer to the 62 period-prevalent cases as *Group A* and the sub-group of 35 incident cases as *Group B*.

I travelled to all renal units on several occasions each to examine medical records (paper and electronic where available) to ensure all cases met ISPD diagnostic criteria including clinical features and either radiological and/or histopathological confirmation (43). Ten cases were excluded because there was another potential cause for their presentation (n=7) or they lacked radiological or pathological confirmation of EPS (n=3). We searched the SRR database (for International Classification of Disease codes; ICD-9/ICD-10) reported in hospital discharge statistics but no additional cases were found. Peritonitis was defined as a PD effluent white cell count above 100 per mm^3.

Statistical analyses were performed using SPSS®. Logistic analysis was undertaken and odds ratios calculated comparing PD duration and probability of developing EPS. Peritonitis rates were calculated as the number of patient months on PD divided by number of infections and expressed as number of months between episodes. The rates were converted to events per person-years for Poisson regression analysis (statistical analysis performed with the help of Jan Kerrssens, statistician NHS Information Services Division, Edinburgh) to test the difference between the groups (relative risk). Survival analyses were performed using the Kaplan Meier method and Log Rank Test whereby p value <0.05 was considered statistically significant.

7.4 Results

7.4.1 Demographics

During the initial study period 1st January 2000-31st December 2007 46 EPS cases were identified; 19 of these were incident patients from the 1238 patients who had commenced PD in Scotland during that study period. Between 31st December 2007 and 30th June 2011 we identified a further 16 EPS cases giving a total of 35 patients from the 1238 incident PD cohort, and 62 EPS cases in total. Thirty-one (50%) were male, 59 (95.1%) Caucasian and median age at diagnosis was 50.6 years (range 23.1-82.3, IQR 41.4-63.8 years).

7.4.2 Diagnosis and timing of diagnosis

There is a significant association between duration of PD and EPS ($p< 0.001$) for group A. The median PD duration before EPS diagnosis (not necessarily continuous) was 5.0 years (range 0.4-12.2 years, IQR 3.0 - 6.4 years). For 1203 patients unaffected by EPS, the median PD duration was 1.3 years (range 1 day - 7.9, IQR 0.6 - 2.5 years) whilst for the 35 affected by EPS the median PD duration was 4.0 years (range 0.4-7.5 years, IQR 2.7-5.3 years) ($p=0.000$). Thirty-eight patients (61.2%) had used automated peritoneal dialysis.

Twenty-four (38.7%) cases had been transplanted before EPS diagnosis and 4 had stopped PD because they received a transplant. In 6 the transplant was still functioning at diagnosis. All transplant patients received calcineurin inhibitor-based (cyclosporin or tacrolimus) immunosuppression. At diagnosis 17/62 (27.4%) were on PD, 61/62 (98%) were diagnosed within 2 years and 55/62 (89%) within a year of stopping PD. Sixteen (25.8%) were diagnosed within 3 months of peritonitis and in 15 (24.1%) this episode was severe enough to merit PD catheter removal.

7.4.3 Clinical Presentation

The most common features are shown in Table 17. All patients had at least one of these three symptoms: abdominal pain, vomiting and abdominal distension (with ascites or with bowel obstruction). Fifty-two cases (83.9%) had diagnostic imaging (*Table 16)* and 38 (61.3%) had a laparotomy or laparoscopy.

Table 17. Most common presenting clinical features and radiological findings of the EPS cases.

Clinical Features *(Most cases had >1)*	**N**	**Imaging Findings (US or CT scan)** *(some cases had >1)*	**N**
Abdominal pain	38	Ascites	41
Vomiting	33	Septate/loculated ascites	25
Weight loss	33	Peritoneal thickening	21
Ascites	19	Peritoneal calcification	12
Elevated Inflammatory markers	20	Bowel obstruction	7
Bowel obstruction	14	Matted/tethered bowel	15
Hypoalbuminaemia	12	Dilated Small Bowel	7
Unexplained anaemia	10		
Bloody ascites/dialysate	5		
Abdominal mass	4		
Diarrhoea	4		

7.4.4 Possible Risk Factors

There was no significant difference between the EPS cases and the PD population who did not develop EPS with respect to age, race, deprivation category, BMI, serum albumin or RRF at the start of PD. Certain primary renal diagnoses (PRDs) are over-represented among the EPS cases namely APKD, FSGS and inherited nephropathies (table 18).

Six (9.7%) patients had no history of peritonitis. For Group A, the median number of peritonitis episodes was 2 (range 0-20, IQR 1 – 4 episodes) equating to 1 episode every 21.3 months PD and for Group B; 1 episode every 20.2 months compared to arate in all PD patients in Scotland 2000-2007 of 1 episode every 20 months (not statistically significant).

In Group A, 19 (30.6%) had documented episodes of *Staphylococcus aureus* peritonitis (1 MRSA), 6 (9.7%) fungal peritonitis and 1 (1.6%) *Pseudomonas* peritonitis. This compared to national average rates of these organisms of 13.7% for SA, 3.1% fungal, and 1.5% for pseudomonas. Of the 4 patients who developed EPS despite under 18 months PD, one had no peritonitis, 2 had 1 peritonitis episode each, caused by coagulase negative *Staphylococci* in both cases and one had 8 episodes of peritonitis caused by recurrent *staphylococcus aureus* (3), CNS (3) or culture negative episodes (2).

Thirty-four patients (54.8%) had used high strength dextrose (3.86%) and 59 (95.2%) had used Extraneal. No patients were treated solely with “bio-compatible” dialysate. Various brands of dextrose-based dialysate were used by the EPS cases. Compared to the remainder of the Scottish PD population, a significantly larger proportion of EPS cases than the remainder of the PD population had stopped PD because of ultrafiltration failure, peritonitis or inadequate dialysis (table 19).

Table 18. Primary renal diagnoses of the incident PD cohort all 62 incident/prevalent EPS cases (Group A) and just the incident EPS cases (Group B) for comparison.

Cause of renal Failure	PD Cohort (n)	PD Cohort (%)	EPS Group A (n)	EPS Group A (%)	EPS Group B (n)	EPS Group B (%)
CRF, uncertain aetiology	215	17.9	12	19.4	8	22.9
Diabetes Type I	183	15.2	4	6.5	4	11.4
Autosomal Dominant Polycystic Kidney Disease	126	10.5*	10	16.1	8	22.9*
Pyelonephritis with urinary tract disease	127	10.6	8	12.9	2	5.7
Renovascular disese	126	10.5	1	1.6		
Chronic GN (unspecified)	67	5.6	4	6.5	2	5.7
Diabetes Type II	66	5.5	1	1.6	1	2.9
IgA nephropathy	62	5.2	4	6.5	3	8.6
Other	56	4.7	4	6.5	1	2.9
Multisystem disorders	52	4.3	1	1.6		
Membranous nephropathy	24	2.0	2	3.2		
Myeloma/light chain deposition disease	21	1.7	1	1.6	1	2.9
Focal segment glomerulosclerosis	15	1.2#	5	8.1	3	8.6#
Drug induced nephropathy	17	1.4				
Amyloidosis	15	1.2				
Herediatry nephropahy	11	0.9*	3	4.8	2	5.7*
Rapidly progressive/crescentic GN	11	0.9	1	1.6		
Membranoproliferative GN	9	0.7	1	1.6		
Total	**1203**	**100**	**62**	**100**	**35**	**100**

**Statistically significant difference p=0.05,*
 # Statistically significant difference p=0.01

Table 19. Reason given in PD audit return for stopping PD (% of patients) comparing incident EPS cases (Group B) and the incident PD cohort. There is no option to list EPS as the cause of technique failure in the PD audit but this was clearly the cause of stopping PD for 8 patients when we examined their case records so the table also lists both EPS and the reason stated on the audit form (hence the column total is 43 and not 35).

Reason for Stopping PD	EPS Cases (N)	EPS Cases (%)	PD Population 2000-2007 (%)	p-value
Peritonitis	15	42.9	20.6	0.03
Ultrafiltration failure	4	11.4	2.4	**0.01**
Inadequate Dialysis	7	20.0	10.1	**ns**
Failed Access	1	2.9	2.5	ns
High Intra-abdominal Pressure	-	-	4.5	-
Transplant	4	11.4	22.2	ns
Patient Choice	-		7.5	
Death	4	11.4	24.4	**0.001**
(EPS	8	22.9	-	-
Total	35	100	100	

Thirty-seven cases (59.7%) were prescribed beta-blockers. We have ACE-inhibitor and angiotensin receptor blocker (ARB) prescription details for 2 units: 19/26 patients (73.1%) were not prescribed either drug whilst on PD, 4 (15.4%) were prescribed an ACE or ARB for the duration of PD and 3 (11.5%) were prescribed one or other for <50% of time on PD.

We had access to complete radiology records for 34 cases; 7 (20.6%) had an MRI scan before EPS diagnosis. As we did not have data with respect to PD dialysate usage, drug therapy or MRI scans for the PD population not exposed to PD we were not able to compare the groups.

Multivariate analysis of potential predictors for EPS

In summary, there were significant differences in the proportion of patients with certain PRDs (APKD, FSGS and hereditary nephropathies (see table 1)) and there were significant differences in cause of technique failure (table 3). However, on multivariate analysis there were no significant predictors of EPS development.

7.4.5 Treatment

Table 20 details the drugs prescribed to treat the EPS cases. Only 4 (6.5%) patients had elective surgical intervention soon after diagnosis, but it is possible that more have gone on to have intervention since the initial data collection, and since the specialist service was set up in Manchester. It was beyond the scope of this retrospective study to assess response to any medical or surgical treatments.

Table 20 Drug therapy prescribed for EPS cases (* for one of the 3 prescribed sirolimus it was commenced as part of post transplant immunosuppressive therapy).

Treatment/Transplant Status	*No. of Cases*
Tamoxifen only	9
Sirolimus	3*
Prednisolone + Tamoxifen	7
Tamoxifen + Azathioprine	1
Prednisolone + Azathioprine	1
Functioning transplant (Tamoxifen added)	6
Transplanted <4 months post-diagnosis	5
Total treated with Tamoxifen	**23**
Total Treated	**32**

7.4.6 Survival

By the 30th June 2011, 42 of the patients with EPS (67.7%) had died. The mortality rate was 46.8% one year after diagnosis. The median survival from diagnosis was 425 days (range 1 – 3962, IQR 106 – 1497 days). From the data it would appear that if patients have survived to 2 years post EPS diagnosis, then their chances of ongoing survival are good (figure 30). Of note, only 8 of the 14 (57.1%) of those presenting with bowel obstruction were dead by 2 years post diagnosis which would suggest bowel obstruction does not necessarily indicate the worst prognosis in our cohort.

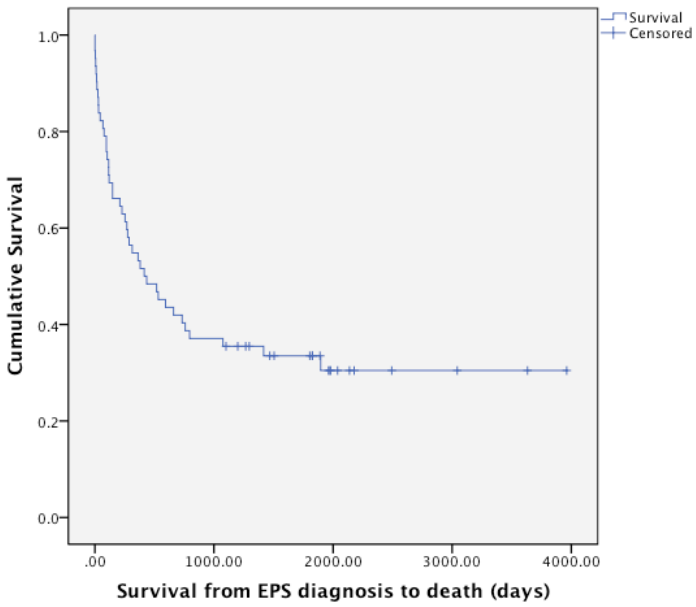


Figure 30. Survival from EPS diagnosis to death for the 62 EPS cases.

However, if we analyse survival for patients from the *start of PD* to death, comparing those who developed EPS and those who did not, it is apparent that the overall survival is comparable with a median of 2382 days for EPS cases (IQR 1599-3513 days) and 2482 days (IQR 880-3413 days) (p=ns) for those who did not develop EPS. However, those who developed EPS had better survival in the first 3 years but thereafter there is a steep fall in survival (figure 31). This reflects the requirement to live long enough to receive sufficient PD exposure to be at risk of EPS and the high mortality rate once diagnosed with EPS.

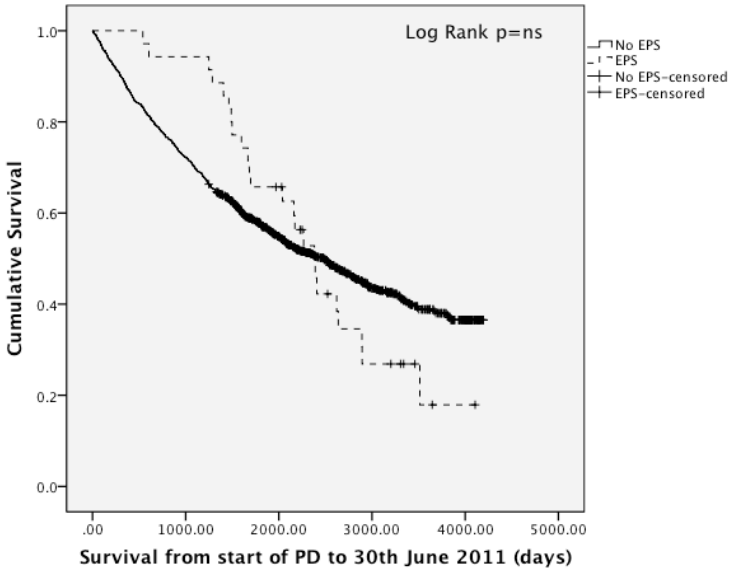


Figure 31. Survival of the 35 incident EPS cases compared to the 1203 incident PD cohort from time of starting PD to death. The data has not been censored for transplantation.

Patients who had a transplant at diagnosis, or who have been transplanted following diagnosis have a much better survival than those who did not receive a transplant (figure 32). There will be survivor bias as patients who died soon after diagnosis would not have had the opportunity to be transplanted, but the survival of the transplanted patients is encouraging.

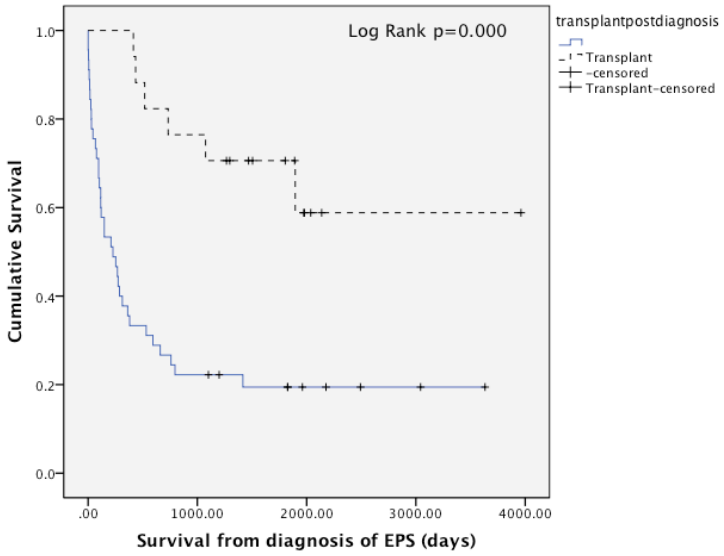


Figure 32. Survival from diagnosis of EPS comparing patients who had a transplant at diagnosis or have been transplanted since diagnosis and the cases who have not.

7.5 Discussion

EPS is an uncommon condition and despite collecting data over an 11 year period, and fully characterising the EPS cases, we have not been able to identify any predictors of EPS development with the data available to us. However in contrast to other studies, by following a clearly defined incident cohort and gathering the majority of our data prospectively, we have an accurate dataset with which to assess clinical presentation and mortality in our population.

7.5.1 Diagnosis and timing of diagnosis

The main presenting symptoms were abdominal pain, vomiting, and/or abdominal distension. In the early case series (1980-1994), 92% of patients had bowel obstruction at some point (30). Only 26% of our cases had evidence of bowel obstruction which is comparable with Summers' study (22%), and slightly less than the Pan-Thames Study (33%) (33, 180).

These data suggest we are diagnosing EPS earlier than in historical studies. Our data support previous reports, with 98% of our cases (61/62) developing EPS either on PD or within 2 years of stopping PD (29-33).

The criteria we used for diagnosis are the international agreed ISPD Guidelines 2000, which have not been formally updated. There has been the suggestion that the criteria be modified, and that EPS may be over-diagnosed if the "milder" cases who do not suffer bowel obstruction are included. We would argue that to exclude "milder" cases would potentially miss the opportunity to intervene and slow the disease process if effective treatments were available. Also, the mortality in our EPS cases was 46.8% at a year after diagnosis, but only of 8/14 patients with bowel obstruction at diagnosis were dead by 2 years post-diagnosis means that those that could be labelled as milder cases, given the absence of overt bowel obstruction, were suffering an equally poor survival. A less dramatic clinical presentation does not necessary equate to a more indolent disease course.

Interest has focussed on the phenomenon of "post-transplant" EPS (181). As we have shown, the majority of EPS cases are diagnosed within the year of stopping PD, and therefore it follows that patients stopping PD for a transplant may still develop EPS. We would argue that in most cases the EPS disease process was already underway but had not yet been diagnosed pre-transplant. However there are reports of EPS being diagnosed several years after stopping PD which raises the question as to whether transplantation or the immunosuppressive drugs may play a role in the pathophysiology in some cases (181). There is evidence that calcineurin inhibitors may promote peritoneal fibrosis which may help explain why patients can develop EPS despite immunosuppression following renal transplantation (182).

There has certainly been interest in whether stopping PD, and therefore leaving the peritoneum "dry" may reduce the opportunity to wash out negative pro-fibrotic factors during the PD exchanges, and somehow accelerate a possibly pre-existent disease process. For this reason some units (Japan) advocate ongoing, intermittent PD exchanges, or peritoneal lavages, after discontinuing PD but there is no evidence that this strategy alters the risk of subsequent EPS development (183).

There appear to be two presentations of EPS. An "acute" presentation following severe peritonitis, with rapid development of clinical features (observed in 24%). This would correspond with Japanese data where 25% of cases appeared to be triggered by peritonitis (29). Other cases followed a "subacute" course, with grumbling symptoms. We believe EPS develops as a result of peritoneal irritation which may come in a variety or combination of forms. If the insult is intense, the fibrotic process may be more aggressive and the clinical course more acute (e.g. following severe peritonitis). If the insult is less intense, but recurrent or persistent, the fibrosis and clinical course may be more insidious.

7.5.2 Potential Risk Factors

The data on potential EPS risk factors are almost exclusively from observational studies, and can only really be interpreted as associations in the absence of well matched case-control data.

Duration of PD is clearly the major risk factor. Whether increased duration causes EPS through *cumulative* exposure to one ongoing (as yet unidentified) pathological trigger or merely increases the risk of encountering a *"one-off"* trigger is not clear.

It is interesting that APKD, FSGS and inherited nephropathies (though very small numbers of these) are over-represented among the EPS cases as causes of PRD. There are no other published data suggesting this association. It could be inferred that as these diagnoses are renal limited, the patients would have above average life expectancy and therefore be more likely to continue PD for long enough to be at risk of EPS than patients with some other diagnoses. However, one might expect other renal limited diseases to be similarly over-represented such as IgA nephropathy, or primary GN but they are not.

Could APKD pre-dispose to fibrosis because of cyst rupture and greater peritonitis risk? We did not find that patients with APKD had a higher rate of peritonitis or specific organisms in our peritonitis analysis, which would go against this argument. Do patients with FSGS, who have abnormal scarring in their glomeruli have a tendency to fibrosis elsewhere and therefore be more likely to develop pathological peritoneal fibrosis? FSGS may be considered primary or secondary to other causes and may therefore be a heterogenous group of patients, but we do not have details of this for our cohort. There is evidence that TGF-β is upregulated in the glomeruli in FSGS and related conditions, which raises the question as to whether TGF-β may be upregulated in general in these patients (184). Further study is warranted to explore this association in more detail.

Previous studies suggest that PD peritonitis may predispose to EPS, particularly if caused by *Staphylococcus aureus*, fungi and/or Pseudomonas (32, 185). Aside from a higher proportion of SA and fungal peritonitis, the peritonitis rates and causative organisms in our EPS cases were comparable to concurrent rates in the Scottish PD population. Six (9.7%) patients had no history of peritonitis, which is consistent with recently published UK data (9.0%) (180).

All except one case had used Extraneal dialysate and the majority required treatment with high-strength dextrose dialysis fluid. It is difficult to untangle whether this reflects ultrafiltration failure in the early stages of EPS, or whether these fluids somehow promote EPS. Unfortunately consecutive peritoneal equilibration test results were not available to help determine the relationship of ultrafiltration failure to use of these products. Despite speculation that Extraneal could contribute to the pathogenesis of EPS, the data published are inconclusive (186, 187).

Although initial reports implicated beta-blockers in the pathogenesis of EPS, recent data, including our own, do not support this theory in relation to beta-blockers currently used (30, 188). ACE-inhibitor and/or ARB drugs may delay peritoneal fibrosis but some of our EPS cases were treated with these drugs (189, 190). Gadolinium contrast is linked to the development of nephrogenic systemic fibrosis, but as only 6 cases had an MRI scan, it is unlikely that gadolinium causes EPS (191, 192).

The relative rarity of EPS and heterogeneity of the PD population makes it difficult to study and identify possible risk factors for EPS. The data so far are largely observational. A Dutch group carried out a case-control study spanning 11 years, comprising 63 EPS cases, and 126 controls matched for date of starting PD and found that ultrafiltration failure, age at start of PD, and time from last transplantation were associated with EPS (193). Given that UF failure is a recognised complication of EPS (which may pre-date diagnosis but almost certainly represents established disease) using its presence as a trigger to stop PD and unlikely to be helpful in reducing the EPS incidence. Age of starting PD or timing of transplantation are generally un-modifiable factors, and certainly more study is required to clarify what the nature of any association is.

7.5.3 Treatment

There are no randomised, controlled trials to guide EPS treatment. Case-series suggest that immunosuppression (prednisolone, azathioprine, mycophenolate mofetil) post-transplant or as specific therapy, can help (29, 33, 175, 194-197). Interest has focussed on tamoxifen which has fibrinolytic properties and encouraging results have been observed (174, 198-200). In Scotland, treatment was inconsistent but tamoxifen was prescribed most often. It was beyond the study's scope to assess treatment response.

Surgery (enterolysis) is associated with variable outcomes and high mortality rates. However, with experienced surgeons, Japan reports impressive results with improved survival using corticosteroids and surgery (167, 168, 170, 201, 202). The rarity of EPS in Europe makes it difficult for surgeons to develop sufficient expertise treatment is centralised to a specialist centre. This has only recently been agreed in the UK, and the specialist centres have not yet published outcome data.

7.5.4 Survival

Patient survival with EPS is poor; the mortality rate for our cohort was 46.8% at one year after diagnosis and 67.7% by the study end. This is consistent with other published case series that quote rates of 37.5% (29) in Japan, 56% (180) and 29.6% (33) in UK series.

The finding that the survival from *start of PD* to patient death is comparable for EPS cases and the PD population in general is perhaps misleading. The PD population as a whole will contain significant numbers of patients who stop PD before they accumulate enough exposure to be at risk of EPS. Therefore patients who develop EPS are likely to have been among the fitter PD patients having survived long enough on PD to get EPS and may be expected to have lived longer than the average PD patient had they not developed EPS.

The survival (figure 31) plot illustrates this whereby the survival lines initially diverge and the EPS patients have a better survival rate until around 4 years when the survival curves converge, then cross (at around 6.5 years) as the EPS cases survival dramatically falls off. This corresponds to the timing of EPS diagnosis and high mortality in the 2 years after diagnosis in the majority of cases. If these patients had not developed EPS the survival curves may be expected to continue at the same trajectory, with the EPS patients continuing to have above average survival.

The survival for EPS cases who subsequently received a transplant is significantly better than those who did not. There is survivor bias in the data, but the flattening of the survival curve post transplant suggests that transplantation also improves survival and would indicate that EPS should not be a contraindication to transplant listing.

In our case series EPS was listed as a contributing cause of death in only 23/42 cases (56%) despite definite pre-morbid diagnosis. It will be difficult to monitor EPS if it is under-recorded in official statistics.

7.5.5 Limitations

Our study was retrospective until January 2006 and prospective until June 2011. Despite this, all case records and electronic patient databases were available for EPS cases to get accurate clinical details of presenting features and patient survival. Drug histories and full radiology records (with respect to previous MRI history) were not complete enough for many patients to be considered reliable and therefore we did not include these unless we were confident we had accurate records. Details for the incident PD cohort are gathered prospectively as part of the national PD audit.

7.6 Conclusions

EPS is associated with duration of PD exposure but there are no readily identifiable risk factors in our population. Diagnosis almost exclusively occurs on PD or within a year of stopping, and may develop following transplantation. Although the mortality from the start of PD to death is comparable for EPS patients and the unaffected PD cohort, this is misleading. EPS carries a dreadful mortality in the 2 years after diagnosis, but thereafter patients seem to fare well, particularly if they receive a renal transplant. While there is no reliable screening test or curative treatment available, clinicians should inform patients of this serious complication of PD and consider alternatives for those with prolonged PD exposure to minimise their risk of EPS.

Chapter 8

What is the Risk of Encapsulating Peritoneal Sclerosis in Scotland?

8. What is the risk of Encapsulating Peritoneal Sclerosis in Scotland?

8.1 Introduction

EPS is uncommon, but the exact incidence is unknown. A UK series identified 27 EPS cases, indicating a rate of 3.3% over 7 years (33). An Australian study identified 54 cases in 14 years, giving a rate of 0.7% (30). Japanese and Korean studies describe rates of 0.8-2.5% (28, 29, 31, 32). Kawanishi et al published 2 year follow-up of a PD cohort in 2001, suggesting an incidence of 0.8% (28). They published a further analysis in 2004 reporting an incidence of 2.5% that is likely to reflect the longer follow up inherent to the study design rather than a true incidence increase (29).

The main motivation for carrying out this study was that other published studies had not reported a true incidence, and were therefore potentially misleading. Most had identified, generally retrospectively, the number of patients developing EPS in a given time period. This would give the incident patients. However, the denominator group included both incident and prevalent patients which does not allow accurate calculation of incidence (28-33). To calculate a true incidence of EPS a cohort of patients must be followed from the start of PD to identify all cases diagnosed *from that cohort* thereafter.

Including incident and prevalent patients in the denominator group will create survivor bias, as only the PD patients who have survived will be included while other patients of the dialysis vintage may have died from EPS prior to the data collection. For patients on PD for more than 5 years the numbers are fairly small, so any bias in this group may have a profound effect on incidence calculations.

In addition, the devastating nature of EPS and the general impression that more cases were being diagnosed locally provided further motivation to accurately quantify the problem in our own population. More than that, if the risk of EPS could be quantified, and if we were able to project the risk of EPS 2, 3 or more years from starting PD this information could be used to counsel patients and guide management.

8.2 Aim

The aim of this study was to report the EPS incidence in patients using PD for end stage renal failure (ESRF) in Scotland between 01 January 2000 and 31 December 2007.

8.3 Methods

The cohort of adult patients who started PD between 01 January 2000 and 31 December 2007 in Scotland (n=1238) was identified from the Scottish Renal Registry (SRR). The 10 adult renal units in Scotland identified potential EPS cases diagnosed on or after 01 January 2000. As detailed in Chapter 6, medical records were examined to ensure all cases met ISPD diagnostic criteria including clinical features and either radiological and/or histopathological confirmation (43). We searched the SRR database (for International Classification of Disease codes; ICD-9/ICD-10) reported in hospital discharge statistics but no additional cases were found. Only incident cases who started PD after 01 January 2000 are used to calculate the EPS incidence.

The initial data analysis was performed in 2008 including incident EPS cases diagnosed by 31st December 2007. We repeated the data collection at intervals until in mid 2011 to include any further cases diagnosed by 30th June 2011, by which point all patients had had a minimum of 3.5 years follow-up from start of PD.

Statistical analyses were performed using SPSS® (version 19). The incidence of EPS was calculated as number of EPS cases divided by number of patients at risk, taking into account the person-time during which events were observed and time elapsed before EPS diagnosis (203). Logistic analysis was undertaken and odds ratios calculated comparing PD duration and probability of developing EPS. Cumulative risks were calculated using the Kaplan-Meier method to plot time from first PD to EPS diagnosis, without censoring for transplantation.

8.4 Results

8.4.1 Incidence and Changing incidence over time

Between 01 January 2000 and 31 December 2007 1238 patients were first exposed to PD. Of these 19 were diagnosed with EPS giving an overall rate of 1.5% in the 8 years to end December 2007 (19/1238). This represented an incidence of 4.9 per 1000 person years or 8.7 per 1000 person years of PD.

Following a further analysis, including all patients diagnosed with EPS up until the 30th June 2009, 31 of the 1238 incident PD patient cohort had been diagnosed with EPS giving an overall incidence of 2.5%.

The last data collection included all EPS cases diagnosed by the 30th June 2011. Surprisingly only a further 4, giving a total of 35, had been diagnosed since the last data collection; the incidence being 2.8% overall. This equates to a rate of 13.6 per 1000 person years of PD.

The rates according to PD exposure are shown in Table 21. Beyond 5 years of PD there is a marked increase in the proportion developing EPS (1 in 7.8 patients at risk).

Table 21. PD exposure for the incident PD cohort and the EPS cases showing the changing numbers between the 3 data collections.

PD Exposure (years)	2008 Analysis			2009 Analysis			2011 Analysis			
	PD Cohort (n)	EPS Cases (n)	Incidence (%)	PD Cohort (n)	EPS Cases (n)	Incidence (%)	PD Cohort (n)	EPS Cases (n)	Incidence (%)	95% Confidence Intervals
≤ 1	480	0	0	470	1	0.2	399	1	0.3	0.0 - 0.8
>1-2	326	2	0.6	327	3	0.9	294	3	1.0	0.0 - 2.1
>2-3	202	4	2.0	198	5	2.5	214	7	3.3	0.9 - 5.7
>3-4	114	4	3.5	117	6	5.1	153	6	3.9	0.8 – 6.9
>4-5	62	5	8.1	63	6	9.5	79	6	7.6	1.2 – 13.4
>5-6	34	3	8.8	35	6	17.1	47	6	12.8	3.3 - 22.3
>6-7	15	1	6.7	17	3	17.6	34	4	11.8	1.0 – 22.6
>7-8	5	0	0	11	1	9.1	13	2	15.4	0.0 – 35.0
>8	-	-	-	-	-	-	5	0	0	-
Total	**1238**	**19**	**1.5**	**1238**	**31**	**2.5**	**1238**	**35**	**2.8**	**1.9 – 3.7**

Table 21 shows the differences in EPS incidence according to PD exposure, but also the changes in the incidence figures between the different data collection and analysis periods. The same data is plotted in figure 1 which shows an apparent fall in incidence between the 2009 data collection and the 2011 data collection for those with >3 years PD exposure. However, the 2011 data show a more linear relationship, highlighting the exponentially rising incidence with increasing PD exposure.

The small numbers of patients on PD beyond 6 years will potentially cause big swings in incidence calculations.

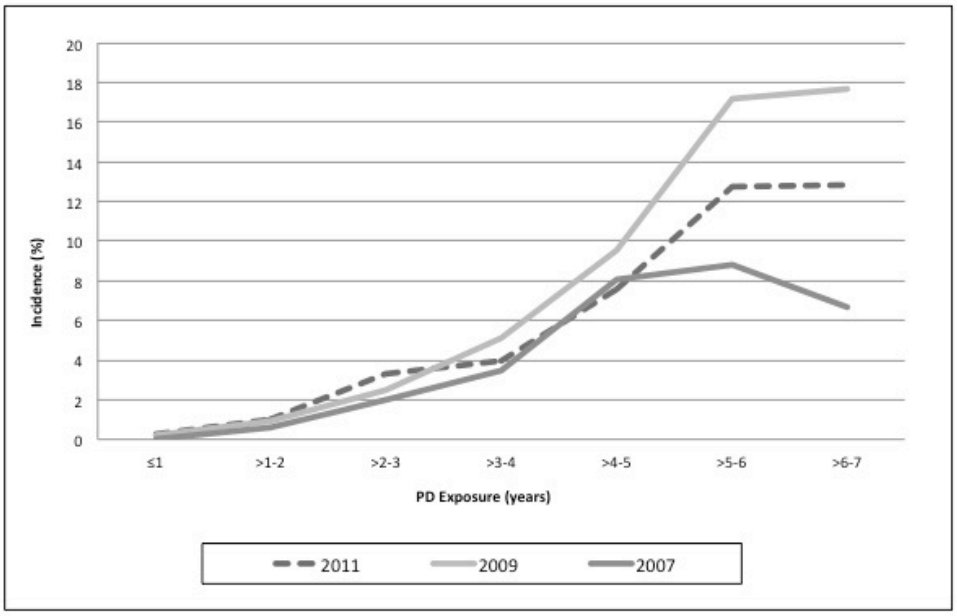


Figure 33. The incidence of EPS according to PD exposure comparing the results from the 3 data collection periods.

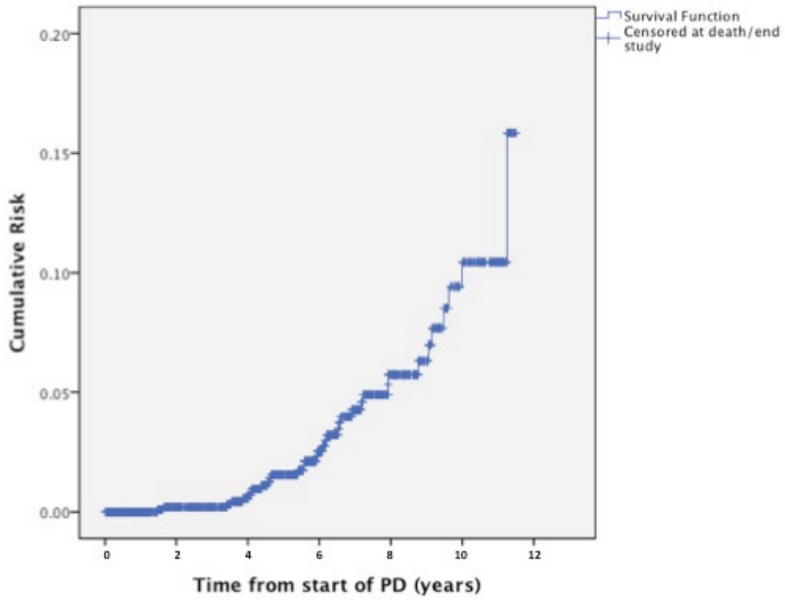
8.4.2 Cumulative Incidence

When a patient commences PD we cannot predict who will continue on PD, who may die or receive a transplant and who will experience technique failure; or the timing of these outcomes. Given that 74.9% of our incident PD cohort (see Technique Failure Chapter) had stopped PD for one of these reasons by 3 years, the number of patients who will receive prolonged PD exposure is small. Therefore, although the EPS risk for all patients who are exposed to 4 or more years of PD is significant, the actual numbers at significant risk of EPS compared to the number of patients started on PD is actually small.

Using the Kaplan Meier method, plotting an EPS-free survival curve from start of PD, regardless of whether the patient continues on PD throughout and only censoring at death or end of follow-up (30th June 2011), it is apparent that by 5 years less than 2% and by 10 years just under 10% of patients will have developed EPS (figure 34).

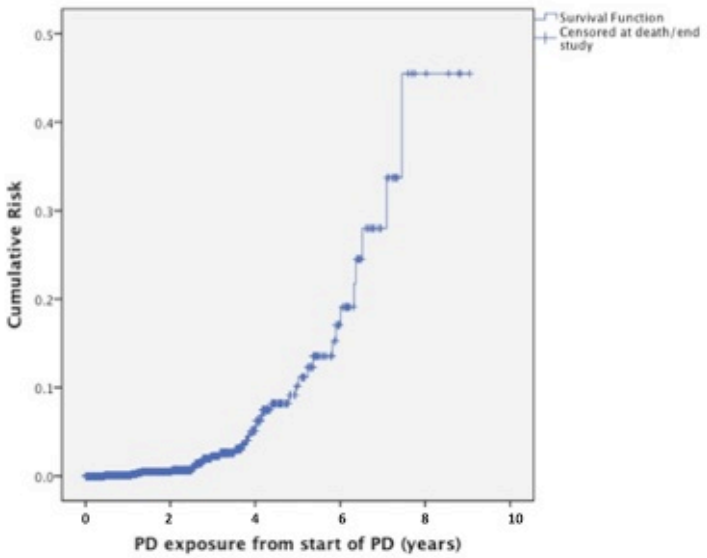
This graph could be used to predict the likelihood of developing EPS at the outset of PD as it incorporates the unknown elements of transplantation, patient and technique survival.

Figure 34. Cumulative incidence of EPS from the start of PD regardless of whether patient contonues on PD or not (censored for death or end of study on 30th June 2011)..



If however we plot the time from start of PD as actual *days spent on PD* therapy, the exponential rise in EPS risk with increasing PD exposure is striking. In practice, as shown in table 1, 15.4% of patients on PD for 7-8 years, and none over 8 years so far have developed EPS. The survival analysis shows us the *accumulated* risk of EPS; if a patient manages to continue on PD for 8 years the cumulative risk of having developed EPS by that point is over 40%

Figure 35. Cumulative risk of EPS with increasing exposure to PD (censored at death, transplantation, transfer to HD or end of study).



8.4.3 Comparison with previous studies

To allow comparison, in Table 22 (last column) we present our data using the same calculation of EPS rate as previous studies (number of EPS cases/incident and prevalent PD patients during study period). The overall incidence using this method of calculation is higher (3.8%) than the actual accurate incidence rate (2.8%) in our population. The 2 studies published by Kawanishi et al in 2001 and 2004 used the same cohort and after longer follow up there are more EPS cases and what appears to be an increased overall incidence. The same pattern is apparent if we compare the data from our study as analysed in 2009, and the most recent data. In addition the overall mortality rate has also increased. These changes reflect the longer follow-up period, and highlight the importance of considering study design and follow-up when comparing studies' results.

Table 22. Using the same method of incidence calculation as previous EPS studies to allow comparison of our study results.

Study	Nomoto *et al* Japan 1996	Rigby *et al* Australia 1998	Lee *et al* Korea 2003	Kawanishi *et al* Japan 2001	Kawanishi *et al* Japan 2004	Summers *et al* UK 2005	Brown *et al* UK *2009*	Brown *et al* UK 2011
Number of EPS Cases	62	54 (46)*	31	17	48	27 (23)*	46	62
Dates of Study	1980 - 1994	1980 - 1994	1981 - 2002	1999 - 2001	1999 - 2003	1998 - 2003	2000-2007	2000-2011
Study Design	Retrospective Multi-centre	Retrospective Multi-centre	Retrospective Multi-centre	Prospective Multi-centre	Prospective Multi-centre	Retrospective Single-centre	Retrospective Multi-centre	Retrospective /prospective Multi-centre
Denominator Population #	6923	7374	3888	2216	1958	810	1588#	1588#
Overall Rate	0.9%	0.7%	0.8%	0.8%	2.5%	3.3%	2.8%	3.8%
Mean PD Exposure (yrs)	5.1	4.3	5.8	10	4.3	6.1	5.4	5.2
Mortality (over study period)	43.5 %	56 %	25.8 %	35 %	37.5 %	29.6 %	56.5%	67.7%

*** Cases** meeting ISPD 2000 criteria in brackets.
# Denominator population includes both prevalent (approximately n=350) + incident PD Patients (n=1238).

8.5 Discussion

We have accurately documented the incidence of EPS in a contemporary incident PD cohort in Scotland. We have also demonstrated the value in ongoing follow-up and repeated data analysis over time to properly quantify the incidence, particularly when the complication being studied is related to duration of PD exposure.

The increase in incidence between the initial data analysis in 2008 and the next analysis in 2011 highlights the importance of accurate data collection, incidence calculation and follow-up. The incidence has increased simply because the cohort's PD exposure has increased, as the risk of EPS is related to PD exposure. Most published prospective studies did not include much follow-up which further limits the reliability of the incidence calculations in addition to the lack of an appropriately defined denominator population.

We can find no convincing evidence in our data collection and analysis to suggest the incidence is rising overall. Indeed fewer patients have been diagnosed in our own renal unit in recent years, and fewer patients were identified in our most recent data collection than the 2009 data collection, which may suggest a decline.

The proportion of patients in the incident PD cohort who were exposed to a particular duration of PD changed during follow-up data collections; more patients had longer PD exposures. Therefore the denominator changes for each incidence calculation when the data are split into PD exposure categories. Beyond 5 years of PD exposure, the numbers of patients are relatively small, the confidence intervals wider and the chances of big changes in incidence from one data collection to another are greater. For example, one more case EPS among the patients with over 8 years PD exposure in the 2011 data collection would change the incidence from 0% to 20%.

The continually changing denominator population and the small numbers of patients helps explain why we have seen significant changes in the EPS incidence particularly beyond 5 years PD exposure. The apparent reduction in incidence between 2009 and 2011 data analysis for those with >5 years PD exposure is probably not a true fall in incidence, but rather statistical anomaly, reflecting the small numbers involved in the calculations. We are confident that the 2011 data collection, by virtue of its longer follow-up period, is the most accurate.

We believe that any "snapshot" analysis of EPS incidence will be liable to such statistical bias. Ensuring adequate follow-up to allow enough PD exposure to the study cohort is essential to minimise this source of inaccuracy. Table 22 comparing our study to previous studies shows the difference that follow-up and alternative methods of calculating incidence can make to study results.

8.5.1 Incidence and Cumulative Risk of EPS

The aim of this study was to report the incidence and establish the risk of EPS for patients starting PD in Scotland. More of our cohort may still develop EPS therefore we report the *minimum* risk of developing EPS when treated with PD in Scotland.

Previous studies suggest that PD duration should not exceed 5 years to try to avoid EPS (32, 33). It is interesting that 5 years has become the widely accepted "cut-off" for acceptable PD exposure, when one of the first studies showed that before 5 years the incidence was significant; Rigby et al quoted rates of 5% at four years (30). The more recent Japanese studies quote much lower rates (<1%) and this has possibly reassured the PD community that EPS is rare before 5 years (29).

However, by 5 years of PD 29/62 (46.8%) of our cases had developed EPS, so stopping PD at 5 years would only potentially avoid just over half of the EPS cases. Our figures suggest that if PD is continued beyond 4 years at least 7.6% will develop EPS, and beyond 5 years 12.1%.

Despite the published evidence that EPS is a significant problem before 5 years, studies still seem to be focussing on the minority of patients who continue PD beyond 5 years; a recent retrospective analysis of a single centre in the USA, only looking at patients with >5 years PD exposure, found an incidence in this population of 14% (204). We believe that although the incidence undoubtedly escalates beyond *5 years*, it is significant enough beyond *4 years* to warrant re-appraisal of ongoing PD treatment for individual patients or at least to prompt discussions with patients to inform them of the risk. We do not know whether the rates in our study represent an increase in the incidence and/or clinical awareness of EPS or if it reflects differences in study design. This makes direct comparison with other studies difficult.

When we started studying the EPS incidence in Scotland, and at the time we published our first analysis, there was a general impression in North America that EPS is rare in their PD population (205, 206). Until recently, relatively little data had been published from North America examining EPS. However, since 2009 there have bee several North American studies that have confirmed that EPS is a much more significant problem than had been appreciated (204, 207, 208). Again the previous under-estimation of the EPS risk is directly related to the methodology of calculating incidence. When units calculate the overall incidence they may only have small percentage of cases (approximately 1% in these studies), particularly if they have a high transplant rate, or high turnover of patients and therefore a disproportionate number on PD for shorter periods (204, 207, 208).

When the same units have split the group and analysed just those patients with PD exposure for example beyond 5 years that they find incidence exceeding 10%. Indeed, Basai et al from an incidence of 1.2% overall, but 15% beyond 6 years, and 38% after 9 years on PD (207). Despite this, studies are still being published that focus on overall incidence, obscuring what may be a significant incidence in subgroups.

To allow a crude comparison of the EPS rate, we used the same methodology as in previous studies (*Table 22*) which suggests the overall rate in Scotland is comparable to recent UK and Japanese studies (29, 33). Given the higher incidence of EPS with shorter PD duration in our and Rigby's series from Australia compared to Japanese studies, future prospective studies should investigate the differences between our countries' practice namely population characteristics, PD prescription/technique and peritonitis details.

8.5.2 Implications of our results for clinical practice

Patients should be informed of risks associated with treatments. Two questions need to be answered: *Should we continue PD for patients established on treatment?* (i.e. what is the risk of EPS if a patient continues on PD treatment having survived on PD for a given time period) and s*hould we start a patient on PD given the risk of EPS?* (i.e. what is the overall risk of developing EPS for a patient before starting PD).

With respect to the first question, our incidence data allows more accurate quantification of the risk of developing EPS for patients already on PD (*Table 1*). After 1 year of PD the EPS risk is almost 0, but after 5 years it is at least 1 in 8. The risk must be interpreted in context; for a patient awaiting cadaveric transplantation after several years of PD the risk of EPS may be considered to be too great to remain on PD, whereas the same risk may be acceptable for an elderly patient with no option of transplantation.

The second question is more difficult to answer. When a patient starts PD it is not known how long they will continue PD or how long they will survive. Although the risk of EPS is significant beyond 4 years, the chance of a patient remaining on PD for 4 years is small, and so the overall risk of EPS is small. The cumulative risk calculates the percentage of patients who have developed EPS by year of follow-up after starting PD regardless of whether they remained on PD or not (*Figure 34*). This allows quantification of the predicted risk of developing EPS.

Although there is general agreement among most Scottish nephrologists that PD should not continue beyond 5 years unless there are exceptional circumstances, it is apparent from the increase in the proportion in our cohort with >5 years exposure between the 2009 and 2011 data collection that this is not necessarily happening in practice. Clearly this is a risk: benefit analysis for each patient.

As we have shown in the patient and technique survival analyses in later chapters of this thesis, the chances of a 75 year old patient being on PD 5 years after starting are very low, and the chances of them living beyond 5 years of starting PD are equally low so decisions about ongoing PD treatment should be made on a case by case basis.

8.5.3 Limitations

If cases have been missed, the incidence we report is an underestimate. To minimise this we performed a search of the national diagnostic records system but found no additional cases.

8.6 Conclusions

Using our data as a guide, the risk of EPS for patients treated with PD in Scotland is near zero after 1 year of PD, but the *minimum* risk after 5 years of PD is 1 in 7.8.

However by factoring in the low probability of such prolonged PD treatment in general, the analysis of cumulative risk is modest at around 2% by 5 years, reflecting the reality that few patients continue PD beyond 3 years. The incidence reported in this study may be used to inform patients of the minimum risk of developing EPS after starting PD.

Chapter 9

Analysis of factors affecting patient survival after commencing peritoneal dialysis in Scotland between 2000 - 2007

9. Analysis of factors affecting patient survival after commencing peritoneal dialysis in Scotland between 2000 - 2007

9.1 Introduction

Patients with renal disease have reduced survival, particularly when end stage renal failure (ESRF) is reached (209). Dialysis patients carry a burden of "traditional" cardiovascular risk factors but unfortunately modification of these risk factors, in contrast with the general population, does not impact significantly on cardiovascular events or death. Dialysis patients also have a range of "non-traditional" risk factors, namely anaemia, increased inflammation, protein-energy wasting, and calcium-phosphate disorders (210-214). Unfortunately there is no evidence yet that attempts to modify these risk factors has any impact on outcomes in peritoneal dialysis (PD) patients (215).

Studies examining potential predictors of poor survival in the PD population have identified several factors that are associated with reduced survival, namely diabetes mellitus (DM) (34, 35, 41, 216), multisystem diseases as a cause of primary renal disease (PRD) (217), peritonitis (17, 97), lower residual renal function (RRF) (24, 37), the rate of loss of RRF (124), older age and lower serum albumin at start of PD (97, 218, 219). Large observational studies have shown that survival is equal on CAPD and APD, but there is evidence that RRF declines more rapidly on APD than CAPD which may theoretically mean increased risk (220-223).

Current study evidence suggests that increasing peritoneal clearance Kt/V >1.7 offers no survival benefit, although a recent ANZDATA observational report suggests survival is optimum at Kt/V 1.7-2.0 (9, 37, 151).

For a variety of reasons the published literature on patient outcomes after starting PD may not be applicable to the current Scottish PD population. Improvements in PD technique in the late 1990s with the introduction of flush before fill/double bag techniques have produced reductions in peritonitis and potentially improved patient outcomes, so survival studies performed prior to these changes are not necessarily relevant to today's patient population (34, 35). Some of the largest registry-based studies from Canada (CORR) and North America (USRDS) and Australia/New Zealand (ANZDATA) span periods of change in PD practice, an important confounder of the results, or there is a delay in reporting results (35, 224, 225). Indeed a recent study examining survival on HD and PD in 35, 265 patients in Canada over 3 time periods (1991-95, 1996-2000 and 2001-2004) have found improved survival in the most recent PD cohorts compared to PD cohorts in the earlier time periods (35). Single centre studies will be liable to centre bias and often have to collect data over many years in order to gather sufficient patients for meaningful analysis (226, 227). Results of studies performed in North East Asia and other non-Western countries with differing patient demographics, clinical practice and lower transplant rates are not necessarily transferable to our population (228). There is a need for contemporary survival data in our own population.

Previous work from the Scottish Renal Registry (SRR) has shown the survival rates on PD and HD are comparable, if not slightly better on PD in the first 24 months in incident RRT patients listed for transplant and who are not diabetic (42). Although there has been debate in older studies, the SRR study's findings agree with other recent studies showing initial survival benefit for PD which changes to survival benefit for HD around 24 months (35-41). Traynor's study covered a 24 year period (1982-2006) but when split into 5 year cohorts, the last of which falls in our study period, the same pattern holds true for each cohort so the findings are applicable to current PD and HD practice (42).

With details of basic demographics (age, gender, PRD, age, dialysis modality) this study also showed that age at starting dialysis and PRD were significant predictors of death. It has been suggested that PD may confer a potential survival benefit by avoiding the "2 day gap phenomenon" of haemodialysis that is associated with an increased mortality but there is little study evidence for this (229).

Beyond this there are no previous studies of patient survival in the Scottish PD population. Since the start of the SRR PD audit in 1999 the SRR contains details for every PD patient treated in Scotland including peritonitis episodes, adequacy data, laboratory results, cause of technique failure, full renal replacement therapy (RRT) history as well as a range of demographic details. With near complete data and follow-up we wanted to quantify patient survival in a recent incident PD cohort and identify potentially modifiable risk factors for death. It was not within the remit of this study to make any further analysis to compare survival on PD versus HD.

9.2 Methods

The SRR collects data from every renal unit in Scotland. Units return data on 2 census dates (30th June and 31st December) each year and thereafter the staff in the registry spend several months checking and clarifying data, particularly if any discrepancies are apparent. For this reason we performed the final search and download of patient data more than 6 months after (March 2012) the end of study date (30th June 2011), to ensure maximum accuracy of the data. Follow-up for the cohort ranges from 3.5 to 11.5 years. We limited data collection to after 2000 as since this time there have been no major changes in PD practice. We analysed data from all incident patients > 18 years old starting PD for the first time between 1st January 2000 and 31st December 2007: 1324 patients in total.

We had details of age, gender, PRD, RRT history, unit, presence of DM or not, deprivation category (SIMD2006 score), date of death and peritonitis details for all patients. We had details of the following variables for the majority of patients: body mass index (BMI) (97.5%), serum albumin within 8 weeks of starting PD (87%), and residual renal function (RRF) measurement within 6 months of commencing PD (78%). Over 95% of the Scottish RRT population is Caucasian.

For analysis the PRD were split into 5 groups (230); primary GN, interstitial nephropathies, multisystem diseases, diabetic nephropathy and unknown/other. To compare clinically relevant groups and compare/plot survival the following variables were split into groups: Serum albumin was split into 3 groups <30, 30-35, >35g/l (whereby 35g/l is the lower limit of normal in Scottish biochemistry departments), and unknown, BMI was split into <20, 20-25, 25-30 and >30 kg/m^2 and age was split into <70 and >70 years at start of PD. RRF was split into 7 groups: anuric, <10, 10-20, 20-30, 30-40, 40-50, >50 l/week/1.73 m^2 but anuric and <10 l/week/1.73 m^2 were comparable and therefore grouped together, and the groups >10 l/week/1.73 m^2 were comparable and therefore grouped together; this left 3 groups <10, >10 l/wk/1.73 m^2 and unknown RRF. However all of these variables were analysed as continuous variables for multivariate analyses.

Not all patients have the same follow-up which is relevant when calculating mortality rates. To calculate mortality rates the population was split according to time since the start of PD or the "potential follow-up time" (if they had all survived): 1 year, 2 years, 4 or more years, 5 or more years, 10 or more years. All patients have 3.5 years minimum follow-up therefore 1 and 2 year follow-up can include all patients, whereas there are progressively fewer patients in the longer follow-up groups. As patients with 10 years follow-up, also have had 5 years (and less) follow-up they are included in all sections.

Therefore the mortality rate = no of deaths in at risk population (e.g. deaths between 0-5 years in those with 5 years follow-up)/number at risk (all patients with 5 years follow-up).

9.2.1 Statistics

Results are expressed as means (and standard deviations) or medians (and inter-quartile range (IQR) or 95% confidence intervals (CI)) for continuous variables, and frequency with percentage for categorical variables. Continuous variables were analysed using univariate analysis (ANOVA) and categorical variables using Chi-squared analysis.

Survival analysis was performed using the Kaplan Meier method using the intention to treat principle, censoring for the date of study end (30th June 2011) and for transplantation only when stated in the figure legend. Patients were not censored for change to HD. Multivariate analysis was performed using Cox proportional hazards model. The covariates included are described in the results section. All statistic analysis was performed using the SPSS statistical software program (version 19). *P values* of less than 0.05 are considered statistically significant.

9.3 Results

9.3.1 Cohort Characteristics

The original incident PD cohort we have been studying comprised 1324 patients. By 30th June 2011, 22 had been lost to follow-up as a result of moving outwith Scotland, and therefore we do not have full details of their subsequent RRT history or survival. These 22 patients have been excluded from the analyses. Of the remaining 1302 patients, 289 patients have received a transplant since starting PD. There is a total of 6446.3 patient years of follow-up.

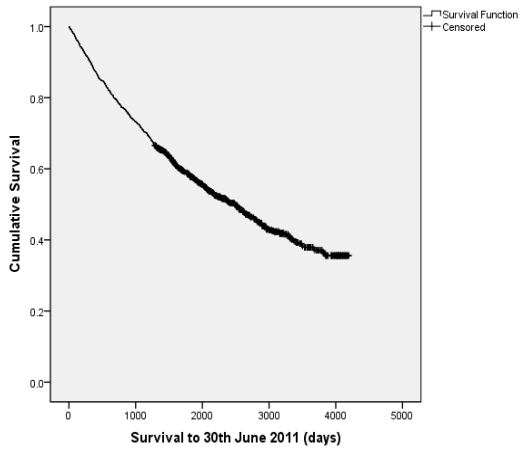
Of the 1302 patients used for analysis, 712 (54.7%) are male, 342 (26.3%) are diabetic. Mean age at starting RRT is 54.4 (SD 16.2, range 14-91 years) and mean age of starting PD 55.0 years (SD 15.8, range 18-91 years).

9.3.2 Survival

By 30th June 2011 675 of the 1302 patients (51.8%) had died. The median survival is 6.8 years (CI 6.2 – 7.5) for the whole cohort, shown in the survival plot (figures 36 + 37). There is marked difference in survival between transplanted and non-transplanted patients that is discussed in a later section. Mean age at death 66.0 years (SD 12.5, range 23-92 years). The mean follow-up for the cohort from start of PD to death or the end of the study (30th June 2011) is 1808.4 days (SD 1104.1), and the median is 1719.5 days (IQR 911-2591, range 2-4196). The mean follow-up for the survivors to 30th June 2011 is 2539.8 days (SD 832.9).

Figure 36 (left). Survival for the whole patient cohort (uncensored)

Figure 37 (right). Survival for the whole cohort, censored for transplantation.



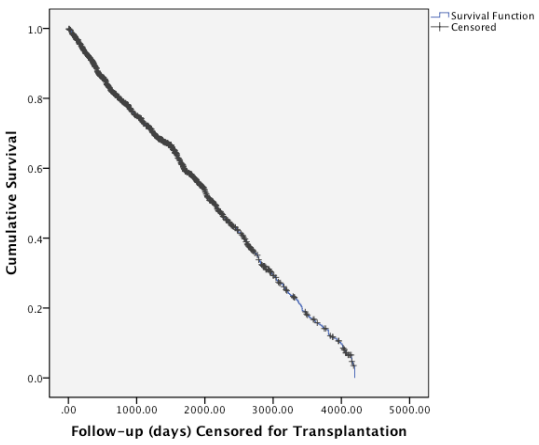


Table 23 shows the differences between the survivors and those dying prior to 30th June 2011. It is apparent that those who have died were older at the start of PD, more likely to be diabetic, less likely to have received a transplant (since starting PD), more likely to have lower serum albumin and lower RRF at the start of PD, and more likely to have had peritonitis. The survivors are more likely to have renal limited PRD (i.e. primary glomerulonephritis (GN) or interstitial nephropathies) than multi-system disorders, DM or unknown/other renal diseases.

Table 23. Comparison of demographics between patients dead or alive by 30th June 2011.

Characteristic	Dead by 30th June 2011	Alive on 30th June 2011	P value
All Patients (n/%)	675 (51.8)	627 (48.2)	-
Transplanted Patients (n/%)	34 (11.8)	255 (88.2)	-
Mean survival/follow-up from start PD (days,SD)	1129.0 (865.3)	2539.8 (832.9)	-
Mean age at start of RRT (yrs± SD)	62.3 (13.4)	45.8 (14.6)	0.000
Mean age at start PD (yrs± SD)	62.8 (12.9)	46.6 (14.2)	0.000
Mean age at death/end study (yrs)	65.9 (12.5)	53.5 (14.0)	0.000
Mean PD duration at death/end study (days, SD)	677.8 (604.4)	823.2 (638.1)	0.000
Male (n/%)	381 (56.4)	331 (52.8)	ns
DM (n/%)	239 (35.4)	103 (16.4)	0.000
Mean Albumin (g/l)* (SD)	33.9 (5.2)	36.7 (4.9)	0.000
Mean RRF (l/wk/1.73m^2)* (SD)	48.3 (40.1)	61.8 (42.8)	0.000
Mean BMI (kg/m^2)* (SD)	25.9 (5.0)	26.2 (4.9)	ns
Peritonitis experienced (n/%)	384 (56.9)	279 (44.5)	0.000
PRD (n/%)			
Primary GN	79 (34.1)	153 (65.9)	
Interstitial Nephropathies	124 (36.0)	220 (64.0)	
Multisystem Disease	164 (68.6)	75 (31.4)	0.000
Diabetic Nephropathy	177 (66.8)	88 (33.2)	
Unknown or other	131 (59.0)	91 (41.0)	

*Measurements taken at the start of PD.

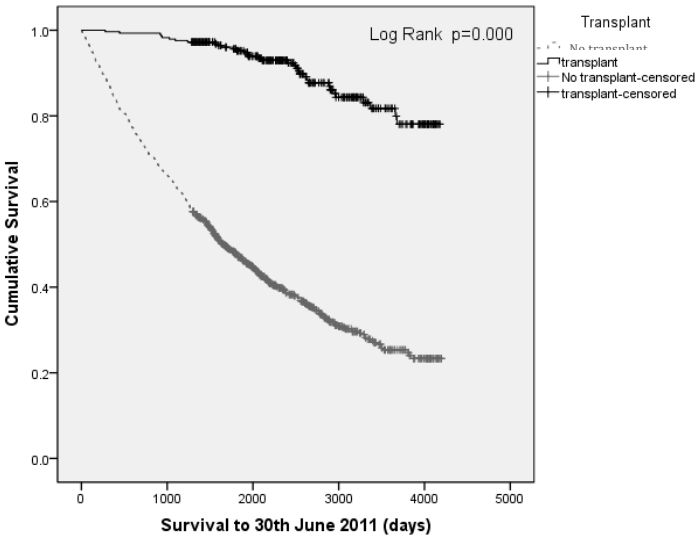
9.3.3 Details of Survival by Subgroups

Given the clear differences in demographic details shown in table 23, further analysis according to different variables was performed. For clarity, relevant multivariate analysis incorporating these variables is presented as a separate section later in the results section.

Transplant

As expected the patients who have received a transplant have a significantly longer survival; median survival for patients not transplanted is 4.5 years and transplanted patients is 6.8 years so far (figure 38).

Figure 38. Survival plot comparing PD patients that did or did not receive a transplant



Patients who received transplants were significantly younger at the start of RRT/PD, less likely to be diabetic, more likely to have a renal limited primary renal diagnosis, have a higher mean albumin and higher RRF as shown in table 24. Interestingly they have significantly longer PD exposure, but lower risk of peritonitis. There is no difference in deprivation categories between those who have been transplanted and those that have not.

Table 24. Comparison between patients who received a kidney transplant and those that did not by 30th June 2011.

Characteristic	Transplanted	Not transplanted	P value
Number of patients	289	1013	-
Dead by 30th June 2011 (n/%)	34 (11.8)	641 (63.3)	0.000
Mean survival PD start to death (days, SD)	2094.0 (895.0)	1077.8 (833.8)	0.000
Mean age at start of RRT (yrs, SD)	42.8 (12.8)	57.7 (15.6)	0.000
Mean age at start PD (yrs, SD)	43.2 (12.7)	58.3 (14.9)	0.000
Mean age at death/end study (yrs, SD)	50.2 (12.7)	62.7 (14.0)	0.000
Mean PD duration* (days, SD)	834.5 (602.4)	723.2 (629.3)	0.005
Male (n/%)	162 (56.1)	550 (54.3)	ns
DM (n/%)	53 (18.3)	289 (28.5)	0.000
Mean Albumin (g/l)*	37.4 (4.5)	34.6 (5.3)	0.000
Mean RRF (l/wk/1.73m^2)*	62.9 (43.0)	52.4 (41.4)	0.001
Mean BMI (kg/m^2)*	25.6 (4.1)	26.2 (5.1)	ns
Peritonitis experienced (n/%)	108 (37.4)	555 (54.8)	0.000
PRD (n/%)			
Primary GN	78 (27.0)	154 (15.2)	
Interstitial Nephropathies	91 (31.5)	253 (25.0)	0.000
Multisystem Disease	30 (10.4)	209 (20.6)	
Diabetic Nephropathy	45 (15.6)	220 (21.7)	
Unknown or other	45 (15.6)	177 (17.5)	

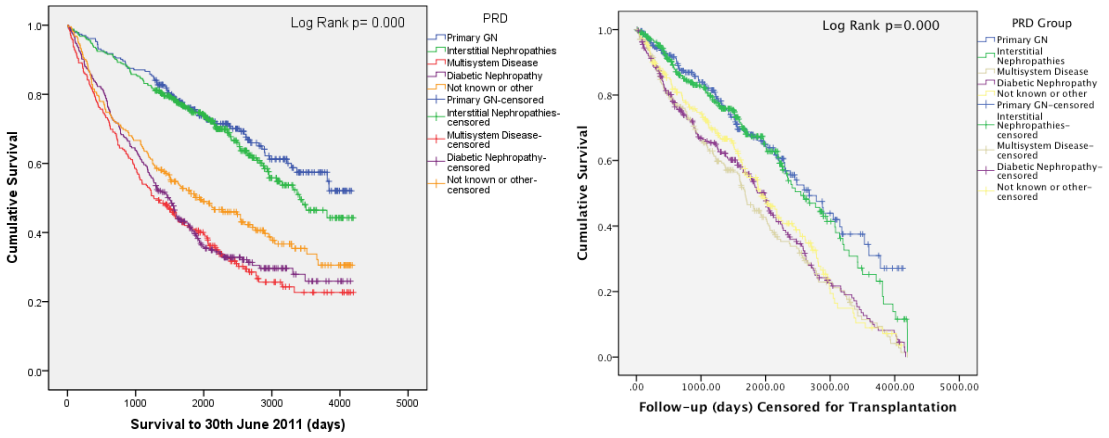
Primary Renal Diagnosis (PRD)

Patients with primary GN and interstitial nephropathies are significantly less likely to have died at the end of the study than those with diabetic nephropathy, multisystem diseases or an unknown cause of renal failure.

On survival analysis, patients with renal limited diseases (primary GN or interstitial nephropathies) have significantly better survival than those with DM or multisystem disorders (figure 39). The difference in survival is less marked when censored for transplantation, reflecting the reality that a greater proportion of patients with renal limited diseases receive transplants (figure 40).

Figure 39 (left). Survival from start of PD comparing PRD groups.

Figure 40 (right). Survival from the start of PD, censored for transplantation comparing PRD groups.



Diabetes Mellitus

Patients with DM have been analysed separately as 76 patients did not have diabetic nephropathy as their PRD. Diabetics have a significantly shorter mean survival as shown in table 25.

Table 25. Differences in baseline characteristics betwen diabetic and non-diabetic PD patients.

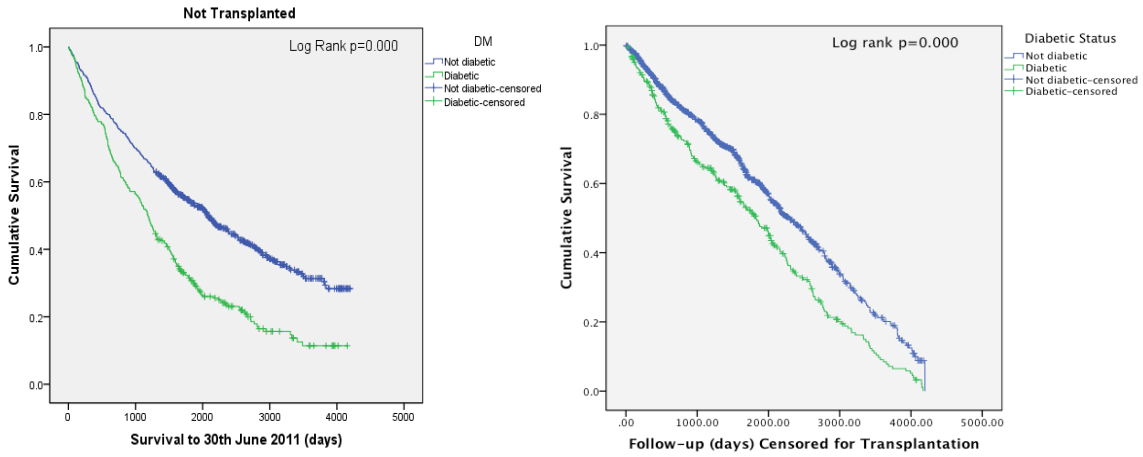
Characteristic	Diabetic	Not Diabetic	P value
Number of patients	342	960	-
Dead by 30th June 2011 (n/%)	239 (69.9)	436 (45.4)	0.000
Mean survival PD start to death (days, SE)	1857 (82.5)	2652 (54.0)	0.000
Mean survival: not transplanted (days, SE)	1527 (78.7)	2255 (61.7)	0.000
Mean survival: transplanted (days, SE)	3636 (143)	3848 (60.8)	ns
Mean age at start of RRT (yrs, SD)	55.5 (14.4)	54.0 (16.8)	ns
Mean age at start PD (yrs, SD)	55.8 (14.2)	54.7 (16.3)	ns
Mean age at death/end study (yrs, SD)	59.9 (13.2)	59.9 (15.1)	ns
Mean PD duration* (days, SD)	601.1 (512.4)	800.1 (652.7)	0.02
Male (n/%)	185 (54.1)	527 (54.9)	ns
Mean RRF (l/wk/1.73m^2)*	61.0 (43.4)	52.9 (41.4)	0.008
Mean albumin (g/l)*	34.3 (5.2)	35.6 (5.2)	0.001
Mean BMI (kg/m^2)*	27.6 (5.1)	25.6 (4.8)	0.000
Peritonitis experienced (n/%)	176 (51.5)	487 (50.7)	ns

*Measurements at the start of PD

Kaplan Meier plots showing the difference in survival between diabetics and non-diabetic patients are shown below (figures 41 and 42). When transplanted patients are excluded or the plots are censored for transplantation it is apparent that <10% of diabetics are alive by 4000 days (11years) compared to >20% of non-diabetics. This is shown in more detail in the mortality section below.

Figure 41 (left). Kaplan Meier plot comparing survival for diabetics versus non-diabetics without censoring for or excluding transplanted patients.

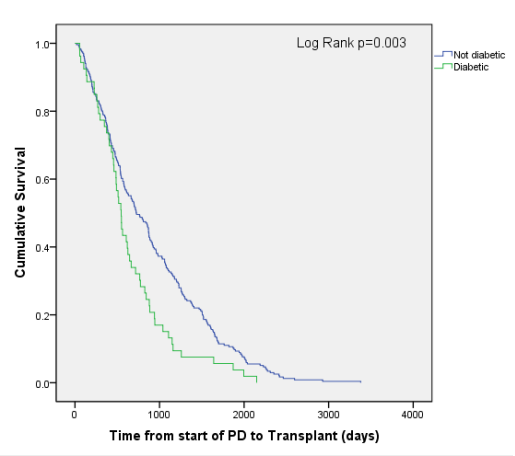
Figure 42 (right). Kaplan Meier plot comparing survival for diabetics versus non-diabetics censored for transplantation

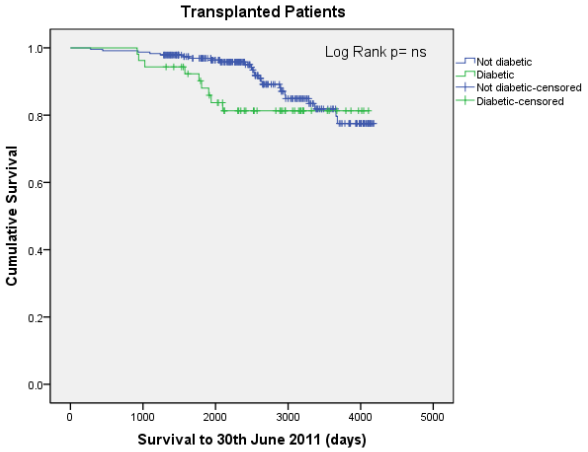


Of note, diabetic patients who are transplanted go on to have comparable survival to non diabetics (table 25). 53 (18.3%) diabetic patients received transplants, of which 33 were combined kidney pancreas transplants, which helps explain why the patients overall survival improves. Indeed when the time from start of PD to first transplant is plotted (figure 43) it is apparent that all transplants in diabetics occur by 2000 days. At 2000 days on the patient survival plot the diabetics' survival curve (figure 44), which had been clearly diverging from non-diabetics' curve, flattens out illustrating the massive survival benefit of transplantation, even in diabetic patients.

Figure 43 (left). Time from start of PD to transplantation: diabetics versus non-diabetics

Figure 44 (right).Kaplan Meier plot comparing survival for diabetic versus non-diabetic patients.





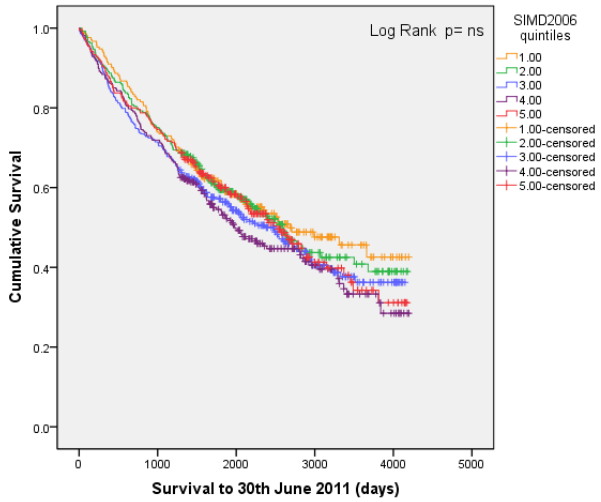
Peritonitis

Patients who had died by the end of June 2011 were significantly more likely to have had peritonitis (p=0.000), but there was no difference in mean time to first peritonitis (321.3 versus 340.9 days, p=ns) or peritonitis free survival. All causative organisms are more likely (though not necessarily statistically significant) to have been experienced by those who subsequently died. However, when analysed as the proportion of peritonitis episodes, gram negative peritonitis is the only organism that is more common in those who subsequently died (70 (18.2%) versus 33 (11.8%), p=0.02), which would be in keeping with their older age (see chapter on Risk Factors for Peritonitis).

Deprivation Category

There was no difference in the proportion of patients surviving according to deprivation category. Kaplan Meier analysis does not show any significant difference in survival but the survival plot shows the lines begin to diverge at approximately 2500 days, with those in more affluent socioeconomic groups having improved survival (group 1= more affluent, group 5= least affluent). There is no difference between groups when censored for transplantation.

Figure 45. Kaplan Meier plot showing survival from start of PD according to deprivation (SIMD2006) quintiles.



Unit

There are no significant differences among units in the proportion of patients who had died by the 30th June 2011 or in the median survival times (Table 26). There is a significant difference in the time to death for those who died, which is shortest in unit 2*. There is no difference in the spread of PRDs, proportion of males, proportion with DM or PD exposure between units.

There is a significant difference in the proportion of patients in each unit from the different socioeconomic groups and the mean age at first PD particularly in unit 10 where patients are substantially older at the start of RRT/PD**.

Table 26. Mortality rates and the demographics of the PD populations in the 10 renal units in Scotland.

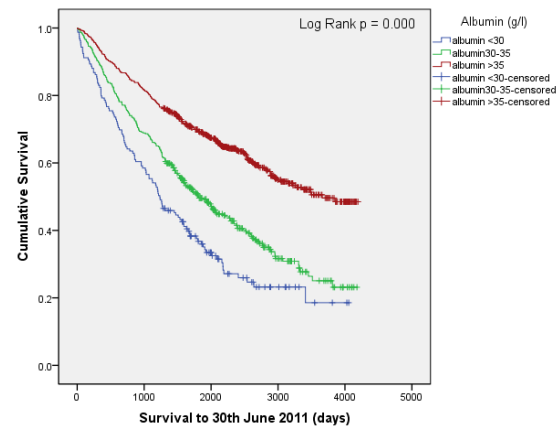
Variable	Unit										P value
	1	2	3	4	5	6	7	8	9	10	
Cumulative PD Patients (n)	132	243	116	85	194	130	95	128	112	67	-
Dead (n/%)*	64 (48.5)	129 (53.1)	57 (49.1)	40 (47.1)	90 (46.4)	71 (54.6)	52 (54.7)	73 (57.0)	54 (48.2)	45 (67.2)	ns
For dead patients mean survival (days, SD)	1375 (1018)	960* (844)	1064 (767)	1214 (712)	1269 (963)	1039 (719)	1045 (879)	1117 (851)	1170 (801)	1192 (951)	0.000
Median Survival Censored for Transplant (days/ IQR)	2263 (920-3149)	2036 (891-3163)	2024 (1506-3481)	2134 (911-3744)	2312 (1261-3195)	1814 (985-3221)	1859 (877-2718)	2046 (1100-3379)	2249 (1269-3425)	2120 (739-2950)	ns
Mean age at start of PD (yrs, SD)	51.9 (15.8)	55.2 (15.8)	55.3 (14.0)	55.2 (16.0)	54.7 (15.7)	49.2 (15.4)	57.9 (15.9)	57.9 (15.9)	53.4 (14.6)	60.4** (17.4)	0.000
Mean BMI (kg/m^2, SD)	25.0 (4.2)	25.5 (4.9)	26.2 (4.3)	26.2 (4.6)	26.2 (5.8)	27.5 (5.0)	26.5 (2.6)	25.8 (4.5)	26.6 (5.5)	26.5 (5.3)	0.02
Mean albumin (g/dl, SD)	37.0 (4.9)	35.9 (5.8)	34.5 (5.2)	35.8 (4.2)	35.1 (5.0)	36.4 (4.6)	35.8 (4.6)	30.7 (4.8)	35.1 (4.4)	35.8 (5.6)	0.000
Mean RRF ($L/wk/1.73m^2$, SD)	62.6 (42.0)	40.3 (34.1)	48.1 (34.7)	61.2 (38.8)	64.7 (59.1)	67.3 (44.3)	65.4 (43.1)	49.0 (34.0)	42.3 (25.3)	64.0 (42.0)	0.000
Deprivation Category (% of population)											
1 (most affluent)	24.4	15.2	15.2	16.7	24.4	18.6	12.8	7.9	15.6	3.0	0.000
2	21.4	14.8	17.0	19.0	21.2	37.2	17.0	22.2	18.3	21.2	
3	36.6	19.0	13.4	20.2	20.7	18.6	25.5	35.7	12.8	39.4	
4	10.7	25.3	20.5	17.9	18.1	12.4	23.4	25.4	32.1	22.7	
5 (least affluent)	6.9	25.7	33.9	26.2	15.5	13.2	21.3	8.7	21.1	13.6	

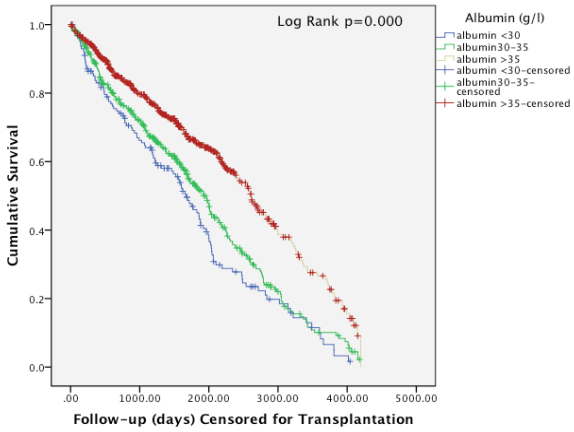
Serum Albumin

When split into groups: albumin >35, albumin 30-35 and albumin <30 g/l, patients with lower serum albumin have poorer survival (see figures 46 and 47). As shown in the chapter *Risk Factors for PD Peritonitis*, patients with a low serum albumin are more likely to be diabetic and older than those with higher serum albumin. Table 27 (below) demonstrates that patients with a lower serum albumin are more likely to die. The mean time to death for patients who died with serum albumin <30, 30-35, and >35 g/l at the start of PD was 920 days (SD 705), 1150 days (SD 846) and 1252 days (SD 846) respectively (p=0.000). The median survival, not censored for transplantation for patients with serum albumin <30, 30-35, >35 g/l at start of PD is: 1234 days (CI 946-1521), 1811 days (CI 1559-2062) and 3660 days (1436-3915) respectively and if censored for transplantation median survival is 1669 days (CI 1423-1915), 1956 days (1778-2134) and 2613 days (2389-2836) respectively.

Figure 46 (left). Kaplan Meier plot showing patient survival according to serum albumin at the start of PD

Figure 47 (right). Kaplan Meier plot showing survival according to serum albumin at the start of PD, censored for transplantation.



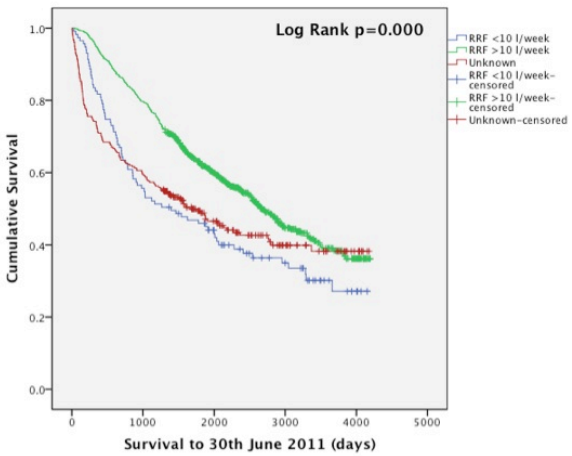


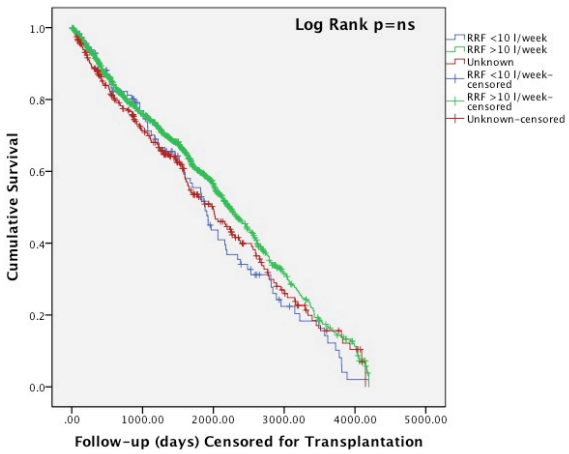
Residual Renal Function (RRF)

Applying the intention to treat principle and not censoring for transplantation, patients with lower RRF at the start of PD have significantly poorer survival as shown in figure 48 (p=0.000). Median survival for patients who have RRF <10, RRF >10 l/wk/1.73m^2 and unknown RRF was 1398 days (CI 655-2140), 2658 days (CI 2446-2869) and 1685 days (CI 1188-2181) respectively (p=0.000).

Figure 48 (left). Uncensored survival from start of PD according to RRF at first adequacy test.

Figure 49 (right). Survival from the start of PD according to RRF at the first adequacy test, censored for transplantation.





Significantly more patients with RRF >10 l/wk/1.73m^2 received transplants (25%, p=0.003) but comparable proportions received transplants in the <10 l/wk/1.73m^2 (18.6%) and unknown (15.1%) groups. If censored for transplantation, there is *no* significant difference between groups.

APD versus CAPD

In the Scottish PD population patients can change from CAPD to APD and back during their PD "careers". The reality that more patients in the latter years of the study have been on APD raises the possibility of an "era effect" influencing outcomes. With this in mind we do not believe that any analysis of APD versus CAPD treatment with respect to patient outcomes would produce meaningful results.

Gender

There is no difference survival between males and females.

9.3.4 Mortality Rate

The mortality rate for the cohort is 51.8% by the end of study or 10.5 deaths per 100 patient years. If transplanted patients are excluded the mortality rate was 63.3% by the end of study period, or 14.6 per 100 patient years. The mortality rate for different time periods is shown in Table 27 below.

If the intention to treat principle is applied, then all patients are included, regardless of whether they are transplanted or not – this allows clinicians to use the data and see what the likelihood of survival is from start of PD, as they cannot know if the patient will receive a transplant or not. For the whole cohort and diabetic patients the figures for survival with transplanted patients excluded are also shown for comparison.

All patients have at least 3.5 years of follow-up since the start of PD. The patient numbers in the first row ("patients with required follow-up") refer to the number of patients who potentially would have had 1,2, 4, 5 and 10 year follow-up if they had all survived that long i.e. the time from starting PD until 30th June 2011. This allows calculation of a true mortality rate (number dead/number with sufficient follow-up).

Table 27. Mortality rates at 1, 2, 3, 5 and 10 years according to baseline patient characteristics.

	Time Period since first PD (years)					
All PD Patients	**1**	**2**	**4**	**5**	**10**	Overall
Patients with required follow-up (n)	1302	1302	1237	1090	271	1302
Patients dead at end of time period (n)	152	274	448	476	177	675
Mortality Rate (%)	11.7	21.0	36.2	43.7	65.3	51.8
Excluding Transplanted patients						
Patients with required follow-up (n)	1013	1013	970	850	215	1013
Patients dead at end of time period (n)	151	272	442	464	167	641
Mortality Rate (%)	14.9	26.9	45.6	54.6	77.7	63.3
Diabetics						
Patients with required follow-up (n)	342	342	333	302	70	342
Patients dead at end of time period (n)	55	102	169	183	55	239
Mortality Rate (%)	16.1	29.8	50.8	60.6	78.6	69.9
Diabetics Excluding Transplanted Patients						
Patients with required follow-up (n)	289	289	282	256	61	289
Patients dead at end of time period (n)	55	102	166	210	53	230
Mortality Rate (%)	19.0	35.3	58.9	82.0	86.9	79.6
PRD: mortality rate (%)						
Primary GN (n=232)	3.9	9.5	18.3	25.8	39.6	34.1
Interstitial Nephropathies (n=344)	5.5	10.2	21.5	26.3	54.9	36.0
Multisystem Disease (n=239)	18.8	33.1	52.4	59.4	82.3	68.6
Diabetic Nephropathy (n=265)	15.5	28.3	49.6	60.3	80.4	66.8
Unknown or other (n=222)	17.1	28.4	43.4	49.5	65.5	59.0
Age: mortality rate (%)						
Age < 70 years at start of PD (n=1053)	8.0	14.9	27.7	35.4	57.5	43.7
Age >70 years at start of PD (n=249)	27.3	47.0	71.4	78.7	98.1	86.3
Peritonitis (mortality rate %)						
No peritonitis (n=639)	14.2	23.5	36.2	42.7	60.2	45.5
Peritonitis (n=663)	9.2	18.7	36.2	44.5	69.6	57.9
Albumin (g/l): mortality rate (%)						
Albumin >35 at start of PD (n=594)	7.2	13.5	26.1	32.8	57.4	40.1
Albumin 30-35 at start of PD (n=389)	11.8	23.7	41.8	52.0	70.5	61.2
Albumin <30 at start PD (n=159)	20.1	35.2	54.9	62.9	88.5	71.1
RRF: Mortality rate (%)						
Anuric	17.9	33.9	44.4	45.3	54.5	64.3
< 10 l/wk/1.73m^2	18.6	39.0	55.9	50.8	72.2	67.8
> 10 l/wk/1.73m^2	5.6	14.3	30.3	39.4	63.7	49.1
Unknown RRF	28.7	36.6	50.6	55.6	70.0	54.8

Diabetics have a significantly higher mortality rate for every follow-up period. Patients with primary GN and interstitial nephropathies have significantly better survival than other PRD groups. Patients with a lower serum albumin, lower RRF and older age at the onset of PD all have increased mortality as do patients who experienced peritonitis at some point.

Multivariate Analysis

The factors associated with reduced survival in our cohort are age at start of PD (p=0.000), having diabetes mellitus (p=0.000), lower serum albumin (p=0.000) and lower RRF (p=0.000) at start of PD, experiencing peritonitis (0.000) and certain primary renal diagnoses (multisystem disorders, diabetic nephropathy, unknown PRD, p=0.000). In addition, transplanted patients had a clear survival advantage. Although there is no difference between units in survival, there are differences in the demographics between the unit populations which may be a confounder. Therefore age, serum albumin and RRF at start of PD, DM status, peritonitis status, PRD, unit, deprivation category and transplant status were included in the Cox Regression analysis.

Significant predictors of survival were *transplant* (HR 0.27, CI 0.18-0.40, p=0.000) *age at start of PD* (HR 1.05, CI 1.04-1.06, p=0.000), *having DM* (HR 1.40, CI 1.2-1.9, p=0.04), *having primary GN* (HR 0.57, CI 0.42-0.79, p=0.001), *having interstitial nephropathy* (HR 0.58, CI 0.42-0.79, p=0.000), *serum albumin at start of PD* (HR 0.96, CI 0.94-0.99, p=0.000) and *RRF at start of PD* (HR 0.995, CI 0.993-0.998, p=0.000).

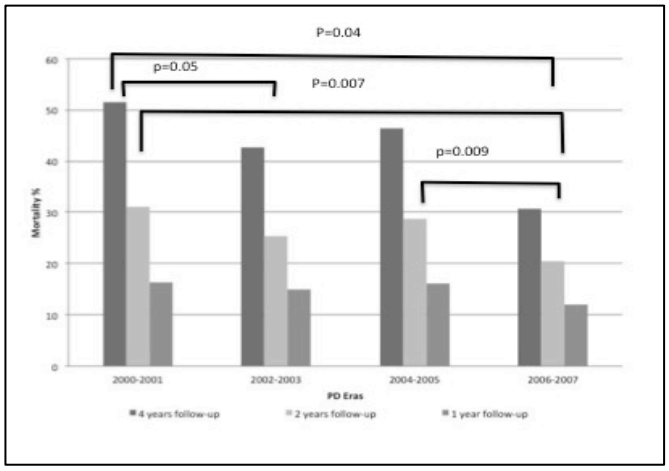
Transplant patients have a 70% lower risk of death than non-transplanted patients. Patients with primary GN have a 43% lower and those with interstitial nephropathy have a 42% lower risk of death than other PRD categories. For each added year of age at the start of PD patients have a 5% increased risk of death. For every g/l increase in baseline serum

albumin patients have a 4% reduced risk of death. For every l0 l/week/1.73m^2 increase in "baseline" RRF patients have a 5% reduced risk of death.

9.3.5 Mortality and Transplantation by PD Era

If split into 2 year cohorts by the date of starting PD (excluding transplanted patients), it is apparent that patients in the most recent cohort 2006-2007 have better 1,2, and 4 year mortality rates than earlier cohorts (see Table 28, Figures 50-51). The most significant differences are between the 2000-2001 cohort versus 2006-2007 cohort which has better 2 year (p=0.007) and 4 year (p=0.04) survival.

Figure 50. 1,2 and 4 year survival rates split into cohorts by PD era.



Comparing the 4 cohorts, the proportion of males and age at starting PD is similar but the 2006-2007 cohort have fewer patients with diabetes and multisystem disease (38.7 versus 44.6% in 2000-2001), more primary GN/interstitial nephropathies (45.1 versus 36.6% in 2000-2001) as well as higher RRF at start of PD (p=0.000). Of note the 2006-2007 has a lower serum albumin compared to the other eras (p=0.000). Therefore the 2006-2007 cohort has a higher prevalence of demographic factors that may be predicted to both improve and reduce survival.

As expected there is difference in survival between patients that were transplanted and those that were not (p=0.0000). Excluding transplanted patients there is still better survival for more recent PD eras (p=0.01), particularly the 2006-2007 cohort.

Figure 51. Survival from start of PD according to era PD began.

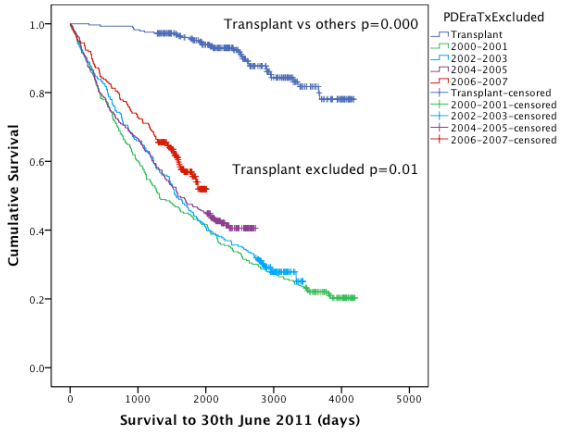


Table 28. Comparison between 2 year cohorts split by PD era.

	PD Era					
	2000-2001	**2002-2003**	**2004-2005**	**2006-2007**	**Transplant Patients**	**Total**
Total Patients (n)	344	305	353	300		1302
Transplanted Patients (n)	68	64	92	65	289	289
Patients (n) by follow-up (excluding transplanted patients)						
1 year	276	241	261	235	289	1013
2 years	276	241	261	235	289	1013
4 years	276	241	261	194	265	972
Mortality (n)						
1 year	45	36	42	29	1	152
2 years	86	61	74	48	3	270
4 years	142	103	121	81	11	447
Mortality Rate (%)						
1 year	16.3	14.9	16.1	12.3	0.35	15.0
2 years	31.2§	25.3	28.7$	20.4§$	1.0	26.7
4 years	51.4*^	42.7*	46.4	41.8^	4.2	46.0
Demographics						**P value**
Age start PD (yrs, SD)	59.5 (14.9)	58.9 (14.7)	56.6 (15.2)	58.3 (14.8)	43.2 (12.7)	0.000
Male (n/%)	159 (57.6)	131 (54.4)	128 (49.0)	132 (56.2)	162 (56.1)	ns
DM (n/%)	77 (27.9)	79 (32.8)	76 (29.1)	57 (24.3)	53 (18.3)	0.002
PRD (n/%)						
Primary GN	45 (16.3)	38 (15.8)	34 (13.0)	37 (15.7)	78 (27.0)	
Interstitial nephropathies	56 (20.3)	59 (24.5)	69 (26.4)	69 (29.4)	91 (31.5)	
Multisystem diseases	69 (25.0)	40 (16.6)	53 (20.3)	47 (20.0)	30 (10.4)	0.000
Diabetic nephropathy	54 (19.6)	60 (24.9)	62 (23.8)	44 (18.7)	45 (15.6)	
Unknown/other	52 (18.8)	44 (18.3)	43 (16.5)	38 (16.2)	45 (15.6)	
Mean serum albumin (g/l,SD)	35.0 (5.2)	35.0 (5.0)	34.9 (5.2)	33.4 (5.8)	37.4 (4.5)	0.000
Mean RRF (l/wk/1.73m^2,SD)	42.4 (32.1)	47.1 (36.3)	57.9 (46.3)	64.5 (46.9)	62.9 (43.0)	0.000

(Chi squared test comparing eras indicated: * p=0.05, ^ p=0.04, §p=0.007, $ p=0.04)

Using Cox regression analysis to compare survival to 4 years (excluding transplant patients and including age at the start of PD, PRD, serum albumin, RRF, and era of PD therapy) the significant predictors were PRD (specifically having primary GN HR 0.60 (CI 0.38-0.94)), RRF (HR 0.996, CI 0.993-1.0). PD era was not shown to be a significant predictor of survival.

9.4 Discussion

In a contemporary cohort comprising all incident PD patients with long follow-up we have identified several factors correlating with mortality, and have confirmed the marked survival advantage conferred by renal transplantation. Although simply characterising our population may help inform clinical practice, ultimately the hope is to identify factors that may be modifiable with a view to improving patient outcomes. Similarly identification of subgroups who do particularly well or poorly on PD, may help guide patient management.

Aside from transplantation and in keeping with previous studies, we have identified age, presence of diabetes, baseline serum albumin and RRF as significant risk factors for death (231). Peritonitis and primary renal diagnosis (both positively and negatively) are also associated with risk of death in our cohort.

9.4.1 Mortality Rates

The median survival in our patient cohort was 6.8 years overall, but 4.5 years if transplanted patients are excluded. This compares to quoted median survival of 4.2 years in Canada (2001-2004 cohort with follow-up to end 2007) (35). The 1 year (84.1%) and 5 year (45.4%) are comparable to USRDS figures of 85% and 40% respectively (46) and 46% (2004-2006) survival at 5 years from ANZDATA report 2011(45).

There is evidence that mortality rates of PD patients elsewhere are improving within the last 17 years (35, 232) and our survival analysis would support this. However, there are several confounding factors in our population and multivariate analysis did not show PD era to be an independent predictor of mortality, despite the significant difference in survival rates on Kaplan Meier analysis.

9.4.2 Transplantation

As expected the patients who have received a transplant have a significantly longer survival, which in part relates to their pre-transplant characteristics as well as the benefits of the transplantation. Patients who received transplants were significantly younger at the start of RRT/PD, less likely to be diabetic, more likely to have renal limited primary renal diagnoses, have a higher mean albumin and higher RRF and therefore are in a much lower risk group even before the transplant proceeds. Interestingly they have significantly longer PD exposure, but lower risk of peritonitis which may relate to the better serum albumin, younger age and lower rate of DM (all of which we have shown to be risk factors for peritonitis in our population). The dramatic levelling off apparent in the survival plots in transplanted diabetic patients further illustrates the massive survival benefit of transplantation.

Unfortunately transplant status is a non-modifiable “risk factor”. There is not an unlimited supply of kidneys for transplantation, and therefore they must be rationed; those with lower co-morbidity are likely to gain more years of life than those with a predicted lifespan already limited by other co-morbidities. However, most would agree that if fit enough for the operation itself, in theory most patients even with co-morbidities would be better off with a functioning kidney transplant.

An Australian group has recently performed modelled analysis to examine the potential survival and economic benefits of deceased donor transplantation in patients of an older age or with co-morbidities (233). They conclude that transplanting younger, healthier patients maximises patient survival and financial gain, but transplanting those with considerable co-morbidity achieves significant survival and cost-saving benefits compared to remaining on dialysis. Unfortunately with over 6,000 patients waiting for kidney transplants in the UK we are far from extending transplantation to higher risk groups (234).

9.4.3 Age

Age at start of PD is a significant predictor of mortality in our cohort as expected (42). Our data show that only 21.3% of patients over 70 years at start of PD are alive at 5 years, which is comparable to ANZDATA results of 25% and 13-25% of patients in the most recent USRDS data (45, 46). Previously, older patients were not listed for transplantation and there has been an increase in transplants in the over 60 years age group; 15% of transplants in 2001 compared to 27% in 2009-2010 went to recipients >60years old (234). Live donor transplantation has made a significant impact on this and it will be interesting to observe how future changes in, for example, paired transplantation contribute to organ allocation. It is conceivable that more elderly patients will receive transplants.

9.4.4 Diabetes Mellitus (DM)

Patients with DM in our cohort have a significantly higher mortality rate with a HR of 1.40 (p=0.000). The higher mortality rate in patients with DM is well-described and our findings are comparable to US data (217). Of note of only 15 diabetic patients surviving 10 years or more in our cohort, 9 have transplants.

Our study examines the outcomes for PD patients only, and we cannot make comparisons with matched HD patients to say whether diabetics may fare better on HD in our population. The SRR study of survival on PD versus HD excluded diabetics to minimise the confounding effects of co-morbidity (42). Certainly there is evidence that older female diabetic patients do better on HD (35) and other studies have shown poorer outcomes on PD versus HD for both sexes with diabetes but current evidence is not sufficient to state that diabetics or diabetic females would definitely survive longer on HD. (34, 228). Thus, beyond transplantation, DM is a non-modifiable risk factor in our population

9.4.5 Primary Renal Disease

Having primary GN (HR 0.57, CI 0.42-0.79, p=0.001) or interstitial nephropathy (HR 0.58, CI 0.42-0.79, p=0.000) as the PRD is associated with >40% reduced risk of death. It is well known that patients with renal limited PRDs such as a primary GN or interstitial nephritis have a lower mortality (46, 217). The assumption is that patients with multisystem diseases or DM succumb earlier to cardiovascular disease, for which they have a higher risk. It is likely that a significant proportion of the "unknown" group presented too late to justify a renal biopsy and will contain a disproportionate number presenting at end-stage, a known risk factor for mortality in our population (230, 235).

9.4.6 Unit, geographical location and deprivation category

There was no significant association between deprivation score and survival in our patient cohort. The survival plots suggest that the curves are diverging but the difference is not statistically significant yet. However, it is known that the more deprived communities in Scotland have poorer survival and life expectancy for the general population is lowest in Greater Glasgow (Units 2+3), Argyll and Clyde (covered by units 2+3) and Lanarkshire (Unit 7) which may be relevant to the shorter time to death seen in these units (236).

There is evidence that PD patients from rural or more remote small towns have significantly poorer survival (HR 1.21) compared to those residing in urban areas (237). Unit 10 has a higher proportion of patients dying by the end of the study. It is in a predominantly rural area compared to most other units but it also has a significantly older mean age for patients starting PD which we have shown is a definite predictor of death in our population. USRDS data shows marked geographical variation in mortality rates but no potential explanation is offered (46).

Patients living further from their parent renal unit have been shown to be at higher risk of morbidity and mortality (238). We did not examine this specifically, but the units covering the more rural and distant locations did not have a higher mortality rates than units with more urbanised geographical areas.

Units' experience of PD certainly affects likelihood of technique failure and infectious complications (217, 239). Larger centre size (cumulative experience >500 patients) versus smaller units (100-199 patients) have a significantly reduced risk of mortality (RR 0.71 versus 0.95) (239). Our data would support this pattern in as much as the unit the with highest mortality hasalso treated the fewest patients during the study period (unit 4). The assumption is that bigger units have more experience which results in better care.

9.4.7 Serum Albumin and related factors

Serum albumin concentration at start of PD correlates with patient survival in our cohort, whereby for every g/l increase in baseline serum albumin there is a 4% reduced risk of death.

The role of serum albumin in renal failure and dialysis-associated mortality is an extensive and complicated subject. It is likely that serum albumin is a surrogate marker of general health in PD patients, influenced by many different potential factors including urinary protein losses, inflammation, acidosis, co-morbidity and fluid overload (240-243). Hypoalbuminaemia has been linked to increased risk of cardiovascular disease and death in PD patients (244). Serum albumin is known to fall in response to illness, as well as being a marker of malnutrition. Malnutrition is well known to affect patient outcomes in ESRF and but more specifically the syndrome of "protein-energy wasting" (PEW) predicts cardiovascular mortality in ESRF and is an area of current research interest (214, 243, 245-247).

Albumin alone is not an accurate measure of nutrition, and should only be used alongside a panel of other measurements (e.g. subjective global assessment, anthropometric measures, BMI, lean body mass) (242, 248, 249). The MDRD Study Group showed that despite strict dietary protein restriction, serum albumin levels did not fall significantly, illustrating that protein intake is not necessarily a significant contributing factor (250). There is a lack of data examining any impact of intervention to improve nutrition in ESRF or RRT patients. Intuitively it seems appropriate to assess nutritional status and UK Renal Association Guidelines recommend regular screening (weekly for inpatients, 2-3 monthly for outpatients when eGFR <20 and 4-6 monthly after start of PD) and involvement of specialist dieticians to optimise nutrition (249). Generally a falling serum albumin in patients approaching dialysis is regarded as evidence that patients are deteriorating and should commence RRT. It is interesting that in our cohort patients with moderate degrees of hypoalbuminaemia (30-35g/l), levels at which clinicians would not necessarily be unduly concerned, continue to have a poor survival many years after the start of PD compared to those with a serum albumin >35g/l.

We have not attempted to quantify the impact that starting PD has on serum albumin levels in this study, but other studies have shown that PD improves nutritional status and serum albumin in most patients, but diabetics are more likely to continue to have poorer nutrition (148). There is good evidence that peritoneal albumin and protein losses do not independently impact upon mortality, but are associated with high transporter status and high co-morbidity scores (251).

9.4.8 Peritoneal Transporter Status

A high peritoneal transporter status has been associated with reduced survival (251, 252) but more recent evidence has contradicted this finding (253, 254). High peritoneal transporter status is also associated with inadequate ultrafiltration, higher peritoneal protein losses and lower serum albumin concentrations which are risk factors for higher mortality, raising the possibility that fast transporter status is a surrogate for these other factors (255, 256). There is debate as to whether it is the peritoneal protein losses rather than peritoneal transporter status that predicts survival (251, 257). We do not have sufficient details to examine this.

9.4.9 Residual Renal Function

We have found that lower residual renal function at the start of PD is associated with increased risk of death; for every 10 l/week/1.73m^2 increased RRF patients have a 5% reduced risk of death. This compares to the CANUSA Study results that showed that for every 5 l/week/1.73m^2 there was a 12% decrease in risk of death, and the NECOSAD-2 study in which each 10 l/week increase in RRF was associated with a 12% reduction in mortality (24, 37).

Without censoring for transplantation, patients in our cohort with lower RRF at the start of PD have significantly poorer survival as shown in the survival plot (p=0.000). When the data are censored for transplantation the oligo-anuric patients have a poorer survival that would be in keeping with previous published data. We have not looked at loss in RRF after starting PD and there is evidence that the rate of loss of RRF is a more potent predictor of survival than single measurements (124, 258).

A recent metanalysis (n=1,079,917 PD and HD patients) examining the influence of GFR at onset of dialysis found no association between GFR and mortality in PD cohorts (259). Lower RRF has been shown to correlate with poorer survival though it is unclear what the mechanism for increased mortality would be. It may be a surrogate measure of patient "fitness", whereby patients who start dialysis later are more likely to have lower RRF, and more likely to be relatively malnourished (260). US data has shown that there is a trend toward starting patients on dialysis earlier, thus with higher GFR/RRF, but it is unclear if this confers benefit to the patient and further studies are required (259). We did not include details of eGFR at start of dialysis so have not examined this.

In PD patients, lower RRF is associated with endothelial dysfunction, which is known to contribute to arteriosclerosis (261). Similarly, hypoalbuminaemia and lower residual renal function have been shown to correlate with excess extracellular water which is thought to be a cardiovascular risk factor (262). Whether this is a causal relationship, and whether it directly influences mortality is yet to be established.

RRF is crucial for PD technique survival as well as patient survival and is a potentially modifiable risk factor. There is evidence that inhibitors of the renin-angiotensin aldosterone system can help reduce peritoneal membrane failure and improve UF/solute

transport in animal models (263, 264). Relatively small human studies have shown that ACE-inhibitors/ARB drugs have a protective effect on the peritoneal membrane, reducing development of fast-transporter status, but there is a need for large scale randomised controlled trials to examine this further (189, 265). There is sufficient evidence to advocate ACE-inhibitor and/or ARB therapy in PD patients, assuming they are not hypotensive as there are other cardiovascular benefits of these drugs in a population at high risk of cardiovascular disease. Certainly there is convincing evidence that preserving residual renal function should be a priority for PD patients.

It is not possible to examine the interplay between serum albumin, urinary and PD protein losses, RRF, nutrition and patient outcomes retrospectively. Detailed prospective studies are required to establish if hypoalbuminaemia results from a modifiable process and whether intervention alters patient outcomes. The many potential causes suggest several potential targets for preventative strategies.

9.5 Limitations

Registry data has inherent limitations namely missing data, potentially fewer clinical details, and a lag time to updating patient details. Unfortunately details of significant co-morbidities have not been collected for the duration of our study, and we do not have details of use of ACE inhibitors/ARB drugs. The relatively small size of Scotland, and close working relationship between registry staff and the PD nurses and doctors from each unit has meant that potential inaccuracies or incomplete audit data are recognised and dealt with in a timely fashion. By allowing an 8 month period to elapse before downloading relevant patient details from the SRR database we have minimised the likelihood of incomplete or inaccurate data. We do not have full details of the cause of death so were unable to examine this.

9.6 Conclusion

We have shown that transplantation, age, DM, PRD, peritonitis, serum albumin and RRF at the start of PD are significant risk factors for mortality in a large contemporary PD cohort with prolonged follow-up. Unfortunately most of these risk factors are not modifiable. With no immediately superior alternative mode of RRT, aside from transplantation, focus should turn to optimising survival for patients choosing PD. Means of preserving residual renal function, reducing or avoiding protein energy wasting, avoiding peritonitis and use of ACE/angiotensin receptor blocking drugs should be the priorities on the basis of current research. Further studies will need to assess whether such interventions translate to survival benefit.

Chapter 10

Future planning; how long can a patient expect to remain on PD in Scotland and what predicts PD longevity?

10. Future planning; how long can a patient expect to remain on PD in Scotland and what predicts PD longevity?

10.1 Introduction

Peritoneal dialysis cannot be continued indefinitely. Even if patients escape early access problems, avoid severe peritonitis, continue to achieve dialysis adequacy targets, and their peritoneal membrane continues to provide sufficient ultrafiltration (UF), continuing PD longterm may now be considered undesirable because the risk of encapsulating peritoneal sclerosis (EPS) increases significantly if PD is continued beyond 4 years (206). In addition survival data suggest that haemodialysis (HD) *may* offer a survival benefit over PD after 2 years. It has therefore been debated that PD should be considered as a short term (2-3 years) treatment (35, 40, 42). The number of patients on PD is falling across the world, as discussed in Chapter 1 Trends in PD, which in part may relate to clinicians' concern that survival is worse on PD, that EPS is an unacceptable risk or because there is less experience of PD in general.

The reality is that transplantation, death and technique failure will conclude most patients PD careers long before they reach the "high risk" exposure for EPS (>4 years).

The average wait for a renal transplant in the UK is currently 1,100 days, just under 3 years (234). Thus a patient waiting for a transplant might expect to need an average of 3 years of an alternative renal replacement therapy (RRT) to bridge the gap. With the rising rate of living donor transplantation, more patients may have a more predictable, and hopefully shorter, duration of RRT before transplantation. Therefore for patients fit enough to be listed for transplantation, the required duration of RRT is likely to be within the widely accepted "limits" of PD exposure.

Mortality rates in dialysis patients are higher than the general population. In the previous chapter we have shown that mortality rates, without censoring for transplantation, are 11.1, 21.0, 36.2, 43.7 and 65.3% at 1, 2, 4, 5 and 10 years in our PD population. When transplanted patients are excluded from the analysis, the equivalent rates are 14.9, 26.9, 45.6, 54.6 and 77.7%. The rates for diabetics and those >70 years at the start of PD are even higher (50.8 and 58.9% at 4 years respectively). Cause of primary renal disease (PRD), residual renal function (RRF) and serum albumin at the start of PD were also significant predictors of death. From this it is apparent that around half of patients will die before they reach 5 years of PD.

The timing of transplantation and death are largely outwith clinicians' control, though it may be possible to predict those most likely to reach these outcomes. In contrast technique failure is potentially modifiable, in as much as rates have been shown to vary between centres and the causes of technique failure may themselves be modifiable (e.g. peritonitis risk) (63, 239). The possible causes of technique failure are shown in table 29. In a large (>30,000 patient) cohort from 1999-2001 in the USA, the main causes of technique failure and transfer to HD were infection (peritonitis and catheter related), catheter malfunction and inadequate dialysis (63). These results are replicated in more recent studies (258).

"Technique survival" refers to duration of PD before it stops for one of the reasons shown in table 29. If comparing studies it is crucial to know if technique survival figures have censored for other outcomes, or if they are crude figures describing the proportion of patients remaining on treatment. For example, Chidambaram et al quote "technique survival" rates of 87.3% at 1 year and 58.2% at 5 years in a specialist centre (266). Similar technique survival rates are quoted in the Japanese literature; 93.6% at 1 year and 68.2% at 5 years (267). However, 44% stop PD by 1 year and 85% by 3 years (266).

If patients stopping PD for reasons other than technique failure are not censored the actual proportion who continue on PD is much smaller. The rate of transfer to HD has been shown to be greatest in the first 6 months of PD, varying between 25-40% (63, 268) (266). Technique failure has not been studied recently in Scotland.

Table 29. Possible reasons for stopping PD.

Reasons for Stopping PD	Reasons for Transfer to HD ("technique failures")
Renal transplantation *Death* *Transfer to Haemodialysis* *Recover renal function* *Withdraw from dialysis*	*Peritonitis* *Inadequate dialysis* *Ultrafiltration failure* *Access issues* *Tunnel/exit site infections* *Complications of raised intra-abdominal pressure* *Fluid leaks* *Patient choice* *Physical/social incapacity*

Possible Risk factors or Predictors of Technique Failure

Various factors have been associated with lower technique survival although not consistently so.

Diabetes Mellitus (DM) only appeared to have a marginal impact on technique survival in some studies, which the authors felt was not likely to be clinically important (63, 269). More recent studies suggest that diabetes has a significant negative impact on technique survival with hazard ratios of 1.32 (CI 1.78-1.48, $p<0.0001$) (266) and 2.82 (258). However in ANZDATA's study of over 12,000 patients, diabetes was associated with a higher rate of peritonitis in the elderly, but was *not* associated with shorter technique survival (270). Both of these latter studies span broad time periods (1995-2005 and 1991-2007 respectively) although sub-analysis to examine any impact of dialysis era did not find any significant differences with respect to technique failure rates. *Age* has been shown to be associated both with improved and poorer technique survival, as well as having no impact at all (63, 266, 269-271).

Male sex (HR 1.13, CI 1.06-1.2, p<0.05) (270) and *obesity* (HR 1.02, CI 1.01-1.03 for every 1kg/m^2) have been shown to be predictors of technique failure (116, 258, 270).

RRT history could conceivably impact upon outcomes in PD patients. Patients with previous renal transplants have comparable rates of technique failure (272).

PD unit, and specifically unit size, may impact upon outcomes, whereby larger units may be a surrogate measure of more extensive PD experience (273). PD units with fewer than 20-25 patients have been shown to have a higher rate of technique failure than larger units (HR 1.13, p<0.0001) (63, 269, 274). Distance from the treatment centre was not shown to impact upon technique failure in some studies (238, 266) but living in a rural location was a associated with reduced technique survival in other studies (275).

Modality may influence technique survival as there is evidence that patients on APD are less likely to transfer to HD, but ANZDATA found no difference between APD and CAPD for technique success (109, 217, 220)

Socioeconomic factors such as patient deprivation have not been studied extensively. Chidambaram et al used education attainment as a proxy for socioeconomic status and found that those living in areas of lower education attainment experienced more technique failure (266). Similarly Mehrotra et al found that patients in areas of lower socio-economic status were more likely to experience technique failure (275). Patients of Aboriginal origin in Australia, who are known to be among the most deprived patients, have a significantly shorter technique survival (HR 1.49, CI 1.32-1.60, p<0.05) compared to other racial groups (270, 276).

Various factors related to the efficiency of PD may impact upon technique survival. *Residual renal function (RRF)* declines over time in dialysis patients and more rapid decline of RRF is associated with shorter technique survival (258). In clinical trials it is apparent that anuric patients have approximately 5-6% lower technique survival than patients with residual renal function (64, 151, 158).

Daily *ultrafiltration (UF)* volumes predict technique survival, whereby UF <1 litre/24 hours is associated with poorer technique survival (277). Similarly, fast *transporter status* has been associated with increased risk of technique failure (and mortality) (252). Emerging evidence suggests that *genetic factors*, specifically variants in the Interleukin-6 (Il-6) gene, may predispose to developing rapid transporter status, so there may be an element of genetic susceptibility to reduced technique survival (278).

Recent interest has focussed on the effect of *PD fluid type*, and in particular the potential for biocompatible fluids to improve outcomes in PD patients. The theory is that biocompatible fluids contain lower levels of glucose degradation products (GDPs) that damage the peritoneal membrane, increase the rate of decline of RRF and potentially increase systemic inflammation which may reduce patient survival (279). The balANZ randomized controlled trial compared biocompatible with conventional PD fluid and found no difference in rate of decline of RRF, but longer peritonitis free survival (15). Icodextrin has been associated with lower risk of technique failure (HR 0.6, CI 0.4-0.92, p=0.018) (280).

10.2 Study Aim

In common with all PD-related studies, those examining technique failure have the same limitations relating to centre effect, country of origin and time-span of study. As techniques have changed (e.g. greater use of APD in Scotland), and the demographic spread of patients has altered (older population), technique success must be regularly re-evaluated. There has been no previous analysis of outcome of PD patients (death, transplantation or technique failure) or technique survival in Scotland. The aim of this study was to analyse the causes and timing of stopping PD and identify any predictors of technique failure in the Scottish population in order to try to answer the question *how long can a patient expect to remain on PD in Scotland and can we predict PD longevity*?

10.3 Methods

The cohort includes all incident patients starting PD (but not necessarily RRT) for the first time between 1st January 2000 and 31st December 2007 and includes details of their PD and RRT history extending to the study end date of 30th June 2011. Patients on PD for <3 months were not excluded as this would miss a substantial number of early technique failures. Although 22 patients have been lost to follow-up by moving outwith Scotland, we have RRT history until that point and have included them in analyses unless stated otherwise, censoring at the date they left Scotland.

Technique failure was defined permanent transfer to HD and was censored for death, renal transplantation, withdrawal of dialysis and recovery of renal function. Patients can transfer between PD and other forms of RRT (transplant or HD) for a variety of reasons. Transfer to HD may occur while there are PD catheter related problems, following peritonitis or if

patients are not able to perform CAPD for whatever reason. From previous studies it is not always clear how these changes in modality are incorporated into the analyses. Traditionally transfer to HD for <60 days would not be considered a technique failure (221). However, most studies do not define whether the technique failure recorded is the final technique failure, or first technique failure. On the basis that true technique failure should be caused by something that precludes future PD treatment, we have analysed the data based upon the final cause of technique failure, but have included details of the average number of separate PD treatment periods the patients experienced.

Patients may transfer from APD to CAPD and back, particularly after peritonitis when most units were routinely transferring patients to CAPD for a period. We felt that attempting sub-analysis looking for differences in outcome on APD versus CAPD would be potentially misleading given these modality switches. The technique survival time for patients who have had more than one period of PD treatment is the cumulative exposure to PD only and does not include time on other modalities of RRT. For the small number of patients still on PD, total PD exposure was censored at the study end 30th June 2011. Deaths are deaths occurring on PD. We have not included patients dying in the 30 days after stopping PD for another reason, as in some previous studies, as a substantial proportion stopped PD because of peritonitis or withdrawal from dialysis and this data would be obscured if we grouped these cases with the deaths.

The causes of technique failure are based upon the cause allocated by the PD nurse completing the audit form. Where there was no cause given, we searched electronic patient databases looking for a cause of technique failure in the diagnosis screens, letters, clinical notes and operation notes. Despite this the cause of technique failure was still not apparent in 31 patients.

Statistical Analysis

Results are described as means and standard deviations (SD) or medians and inter-quartile ranges (IQR) as appropriate. Proportions of categorical data were compared using Chi-squared analysis. Continuous data were analysed using ANOVA. Duration of PD before stopping and comparisons between groups were analysed using Kaplan Meier analysis. The analysis was performed in stages; firstly to look at the causes of stopping PD (transplant, death, technique failures, withdrawal) and potential predictors of these outcomes or the timing of the outcome. Thereafter analysis focussed on technique failure: predictors for the causes of technique failure (peritonitis, inadequate dialysis, UF failure, access issues, high pressure complications, fluid leaks, patient choice) and timing of technique failure. Lastly, combined data for patient outcome for clinically relevant subgroups are shown as percentages of patients remaining on PD after 1,2,3,4, and 5 years.

10.4 Results

10.4.1 Cohort Characteristics

The study cohort consists of 1324 incident PD patients. Of the 1324 patients, 932 (70.4%) had one continuous episode of PD (transfer to HD <60 days not considered a break) and of the remaining 392 patients, 25 had an interruption to PD following a transplant which subsequently failed. The remainder were on HD for varying periods between PD episodes. Of the 22 patients ultimately lost to follow-up, 9 had stopped PD before leaving Scotland, therefore outcome of PD is not known for 13 patients. Only thirty-eight patients in the 2000-2007 cohort were still on PD at the end of the study. Of the 1324 patients, 432 (32.6%) had RRT prior to starting PD; 43 (3.3%) had had a renal transplant (median duration 13 yrs, IQR 142 days – 17 years) and 389 (29.4%) had had HD (median duration 59 days, IQR 26-178 days). The cohort comprised 54.6% males, 26.3% diabetics, mean age at the start of PD 54.9 years, and 50.5% experienced peritonitis at some point.

10.4.2 Outcome of PD

The most common reasons for stopping PD are transfer to HD (technique failures) (47.3%), death (23.3%) and renal transplantation (22.5%). Details of the reasons for and timing of stopping PD are shown in table 30. By 3 years, 73.9% of patients have stopped PD. The majority of technique failures are in the first 2 years (60.8%).

Table 30. Reasons for and timing of stopping PD and causes of technique failure.

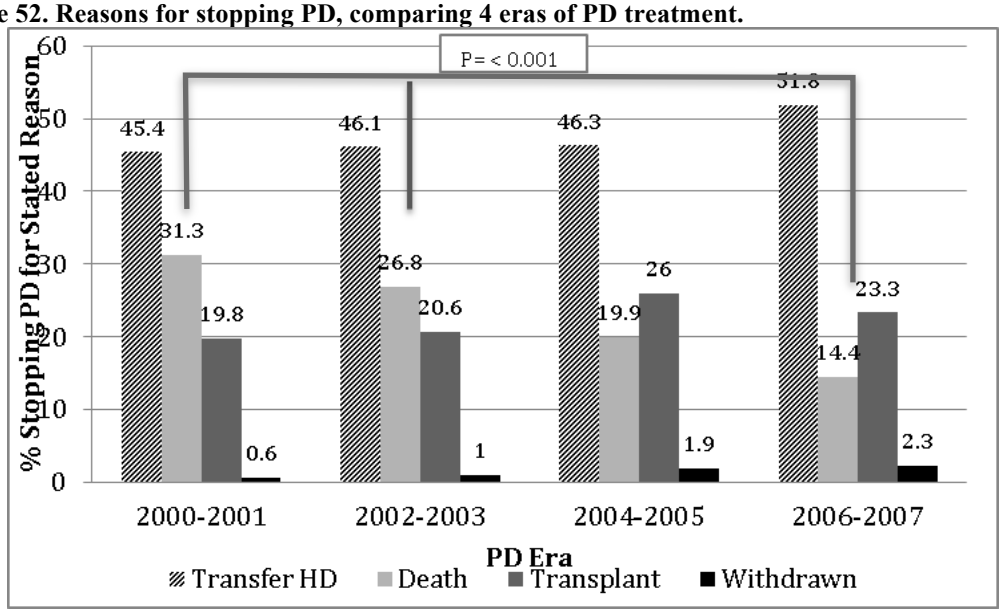
	Total (n/% of all)	Duration of PD before stopping (months)					
		≤3	> 3-12	>12-24	>24-36	>36-60	>60
1311 patients with follow-up, number stopped PD (%)	1273[$] (97.1)	131 (10.0)	317 (24.2)	302 (23.0)	219 (16.7)	218 (16.6)	86 (6.6)
Cumulative total (n/%)	1273[$] (97.1)	131 (10.0)	448 (34.2)	750 (57.2)	969 (73.9)	1187 (90.5)	1273 (97.1)
Reason PD Stopped (n/% of individual cause)							
Transplant	298 (22.5)*	9 (3.0)	61 (20.5)	90 (30.2)	54 (18.1)	58 (19.5)	26 (8.7)
Dead	308 (23.3)*	30 (9.7)	84 (27.3)	65 (21.1)	47 (15.3)	60 (19.5)	22 (7.1)
Recovered function	22 (1.7)*	6 (24.3)	8 (36.4)	4 (18.2)	4 (18.2)	0	0
PD Withdrawn	19 (1.4)*	3 (15.8)	4 (21.1)	6 (31.6)	2 (10.5)	3 (15.8)	1 (5.3)
Lost to follow-up	13 (1.0)*	4 (30.4)	3 (23.1)	3 (23.1)	0	2 (15.4)	1 (7.7)
Transfer HD	626 (47.3)*	83 (13.3)	160 (25.6)	137 (21.9)	112 (17.9)	97 (15.5)	37 (5.9)
Reason transferred to HD (n/% of each cause)							
Peritonitis	268 (42.9)[§]	24 (9.0)	72 (26.9)	68 (25.4)	41 (15.3)	48 (17.9)	15 (5.6)
Inadequate Dialysis	138 (22.1)[§]	8 (5.8)	29 (21.0)	30 (21.7)	37 (26.8)	26 (18.8)	8 (5.8)
UF Failure	37 (5.9)[§]	5 (13.5)	3 (8.1)	3 (8.1)	12 (32.4)	5 (13.5)	9 (24.3)
Access problems	38 (6.1)[§]	20 (52.6)	6 (15.8)	6 (15.8)	3 (7.9)	2 (5.3)	1 (2.6)
Fluid leak	19 (3.0)[§]	9 (47.4)	6 (31.6)	2 (10.5)	1 (5.3)	1 (5.3)	0
High pressure	9 (1.4)[§]	1 (11.1)	5 (55.6)	1 (11.1)	1 (11.1)	1 (11.1)	0
Patient choice	47 (7.5)[§]	7 (14.9)	17 (36.2)	7 (14.9)	9 (19.1)	5 (10.6)	2 (4.3)
Tunnel/exit site infection	11 (1.8)[§]	2 (18.2)	4 (36.4)	4 (36.4)	1 (9.1)	0	0
Abdominal surgery	10 (1.6)[§]	2 (20.0)	3 (30.0)	3 (30.0)	2 (20.0)	0	0
Social/Physical Reasons	18 (2.9)[§]	1 (6.7)	6 (33.3)	6 (33.3)	1 (6.7)	3 (16.7)	1 (6.7)
Unknown	31 (2.3)[§]	4 (12.9)	9 (29.0)	7 (22.6)	4 (12.9)	6 (19.4)	1 (3.2)

[$] Note that 1324 patients in total, but 13 lost to follow-up and excluded from calculation and 38 still on PD at the end of study so cumulative row total=1273. * The percentages in this column refer to the proportion of the total population experiencing this as the cause of stopping PD. [§]These percentages refer to the contribution of each cause to total PD technique failure. All other percentages refer to the proportion of the individual cause of stopping PD occurring in each time period (e.g. 26.9% of all technique failures caused by peritonitis occur between 3-12 months, with row total=100%) rather than the percentage contribution to all technique failures in that time period.

Influence of PD Era and PD unit upon outcome of PD

There is a difference between PD eras, with patients being less likely to die on PD ($p<0.001$) and more likely to transfer to HD (p=ns) in 2006-2007 versus 2001-2002 and 2002-2003 eras. The causes of technique failure are stable, aside from an increased proportion attributed to inadequate dialysis in 2006-2007 (23.4%) compared to 2000-2001 (19.0%) (p=ns) (figure 52).

Figure 52. Reasons for stopping PD, comparing 4 eras of PD treatment.



10.4.3 Cause of Technique Failure

The causes of and timing of PD technique failure are detailed in table 30. The main causes of technique failure are peritonitis (42.9%) and inadequate dialysis (22.1%). As expected the majority of technique failures attributed to access issues (52.6%) and fluid leaks (47.4%) occur in the first 3 months as these problems tend to declare themselves early. Although small numbers, tunnel/exit site infections cause problems within the first 2 years (90.9%). UF failure is more of a problem later in dialysis, with 70.2% of cases occurring >2 years of PD. Peritonitis and inadequate dialysis occur in similar proportions across the time periods, causing few technique failures <3 months (<10%) and >5 years (<6%). Interestingly half (51.1%) of patients who choose to stop PD, do so within the first year.

There are differences between units in the reasons for stopping PD (table 31). In unit 3 patients are more likely to be transferred to HD (59.3%) than stop PD because of death (13.6%) (p=0.01). Aside from units 3 (59.3%) and unit 10 (36.8%), other units are comparable to the national average (range 38.5-51.9%) for technique failure. Once data are split by cause of technique failure, the numbers are too small for most categories to make valid comparisons. The variability in cause of technique failure does not clearly link to unit size.

Table 31. Outcome of PD and causes of technique failure by unit.

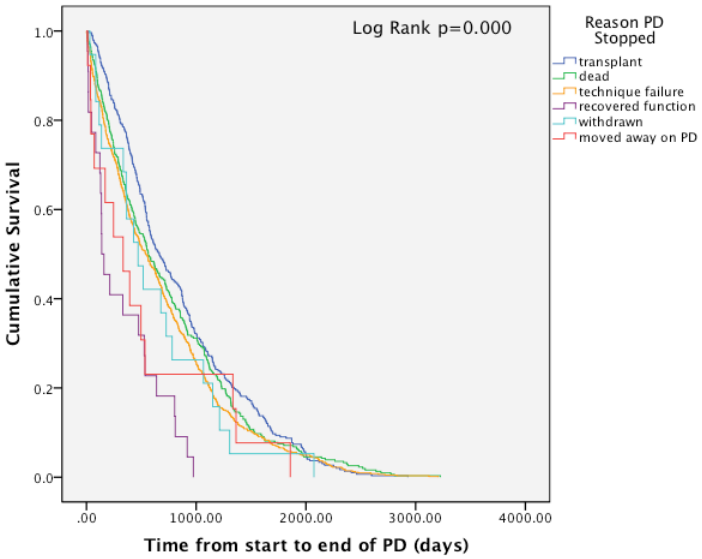
Reason PD Stopped	**Unit**										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**P value**
Transplant	37 (27.8)	53 (21.5)	24 (20.3)	14 (16.3)	50 (24.9)	25 (18.8)	29 (30.2)	21 (16.0)	31 (27.7)	14 (20.6)	0.000
Dead	22 (16.5)	71 (28.9)	16 (13.6)	18 (20.9)	35 (16.9)	34 (25.6)	26 (27.1)	33 (25.2)	31 (27.7)	23 (33.8)	0.000
*Recovered function**	1 (0.8)	7 (2.8)	4 (3.4)	2 (2.3)	1 (0.5)	1 (0.8)	2 (2.1)	0	1 (0.9)	3 (4.4)	-
*PD Withdrawn**	1 (0.8)	0	0	2 (2.3)	10 (5.0)	3 (2.3)	1 (1.0)	4 (3.1)	0	2	-
*Still on PD**	4 (3.0)	4 (1.6)	4 (3.4)	5 (5.8)	11 (5.5)	2 (1.5)	0	3 (2.3)	5 (4.5)	0	-
*Lost to follow-up**	0	0	0	1 (1.2)	4 (2.0)	3 (2.3)	1 (1.0)	2 (1.5)	0	2 (2.9)	-
Transfer HD	68 (51.1)	111 (45.1)	70 (59.3)	44 (51.2)	91 (45.3)	68 (51.1)	37 (38.5)	68 (51.9)	44 (39.3)	25 (36.8)	0.000
Cause of technique failure											
Peritonitis	23 (33.8)	56 (50.9)	23 (32.9)	19 (43.2)	38 (41.8)	35 (52.5)	11 (29.7)	39 (57.4)	19 (45.2)	5 (19.2)	0.000
Inadequate Dialysis	19 (27.9)	17 (15.5)	26 (37.1)	12 (27.3)	21 (23.1)	9 (13.2)	13 (35.1)	7 (10.3)	6 (14.3)	8 (30.8)	0.000
*UF Failure**	5 (7.4)	9 (8.2)	6 (8.6)	0	3 (3.3)	4 (5.9)	6 (16.2)	2 (2.9)	0	2 (7.7)	-
*Access problems**	1 (1.5)	5 (4.5)	7 (10.0)	3 (6.8)	11 (12.1)	1 (1.5)	2 (5.4)	2 (2.9)	4 (9.5)	2 (7.7)	-
*Fluid leak**	3 (4.4)	4 (3.6)	4 (5.7)	0	2 (2.2)	1 (1.5)	0	4 (5.9)	1 (2.4)	0	-
*High pressure**	0	2 (1.8)	2 (2.9)	1 (2.3)	1 (1.1)	0	2 (5.4)	0	1 (3.8)	0	-
*Patient choice**	4 (5.9)	9 (8.2)	1 (1.4)	6 (13.6)	8 (8.8)	6 (8.8)	1 (2.7)	6 (8.8)	4 (9.5)	2 (7.7)	-
*Tunnel/exit site infection**	0	1 (0.9)	0	0	1 (1.1)	4 (5.9)	0	2 (2.9)	2 (4.8)	1 (3.8)	-
*Abdominal surgery**	2 (2.9)	2 (1.8)	0	0	1 (1.1)	0	0	2 (2.9)	1 (2.4)	2 (7.7)	-
*Physical/social reasons**	3 (4.4)	2 (1.8)	1 (1.4)	1 (2.3)	3 (3.3)	1 (1.5)	2 (5.4)	2 (2.9)	0	1 (3.8)	-
*Unknown**	8 (11.8)	3 (2.7)	0	2 (4.5)	2 (2.2)	7 (10.3)	0	2 (2.9)	5 (11.9)	2 (7.7)	-

* Patient numbers are too small in these categories to make Chi-squared analysis valid.

10.4.4 PD Survival by outcome

When plotted (figure 53), the major causes of stopping PD follow an almost identical trajectory, with median duration of PD before stopping 664 days (IQR 379-1164) for transplant, 541 days (203-1015) for transfer to HD and 564 days (243-1117) for death.

Figure 53. Kaplan Meier plot showing time to stopping PD comparing reasons for stopping.



10.4.5 Technique Survival overall and by underlying cause

When censored for death, transplantation, loss to follow-up and the study end date, the median technique survival is 1113 days (IQR 482-2153) (figure 54+55). When analysed by cause of technique failure, figure 55 and Table 32 reinforce the message that UF failure mainly presents after 2-3 years of PD while peritonitis and inadequate dialysis show an almost linear relationship with PD duration/technique failure.

Figure 54 (left) Technique survival censored for death, transplantation and study end date

Figure 55. (right) Technique survival comparing cause of technique failure

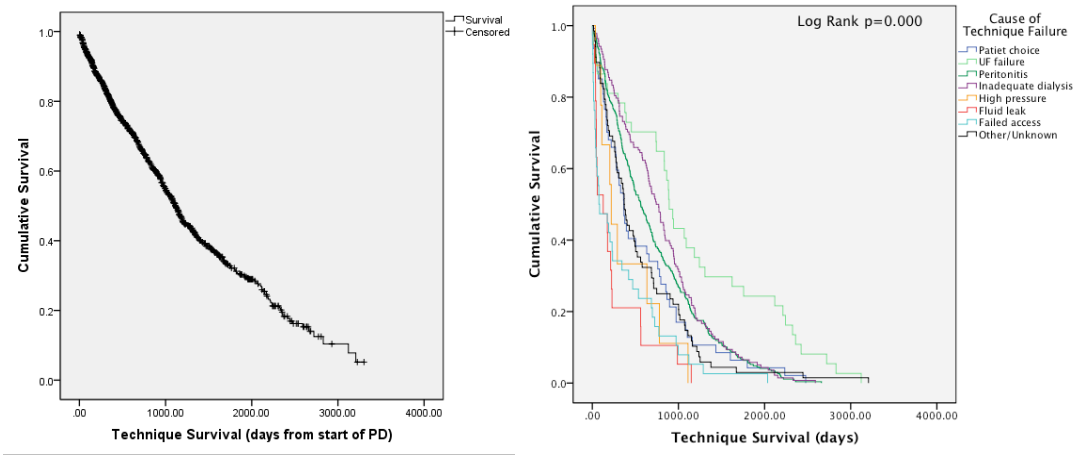


Table 32. Mean and median time from start of PD to stopping PD or being lost to follow-up.

	Time to Stopping PD (days)	
	Mean (SD)	**Median (IQR)**
All Patients (n=1324)		586 (253-1112)
Reason PD Stopped		
Transplant	833 (600)	664 (379-1164)
Dead	746 (633)	564 (243-1117)
Recovered function	329 (322)	139 (84-534)
PD Withdrawn	627 (535)	470 (110-1066)
Lost to follow-up	530 (601)*	334 (70-533)*
Transfer HD	689 (602)	541 (203-1015)
Reason transferred to HD	**Mean (SD)**	**Median (IQR)**
Peritonitis	711 (34.9)	562 (277-1071)
Inadequate Dialysis	802 (47.0)	742 (318-1087)
UF Failure	1139 (147.7)	892 (393-1757)
Access problems	336 (74.7)	78 (31-536)
Fluid leak	251 (76.0)	127 (45-229)
High pressure	387 (123.1)	221 (112-635)
Patient choice	580 (85.0)	365 (159-866)
Tunnel/exit site infection	404 (84.8)	291 (87-579)
Abdominal surgery	449 (115.1)	275 (140-711)
Unknown	666 (119.2)	404 (185-1078)

*Mean/median time patients were lost to follow-up

10.4.6 Possible Predictors of PD outcome

We have shown the causes and timing of stopping PD in our cohort but it would be useful to be able to predict these outcomes and when they may occur for specific patients. We will now present data showing possible predictors for each of the three major PD outcomes, transplantation, death and technique failure. Technique failure is presented in more detail given the multiple potential causes.

10.4.6.1 Transplantation

As shown in the Patient Survival Chapter, patients who received transplants were significantly younger at the start of RRT/PD (mean age at start of PD 43.2 versus 58.3 years for non-transplanted patients, p=0.000), less likely to be diabetic (18.3 versus 28.5% for non-transplanted patients, p=0.000), more likely to have renal limited primary renal diagnoses (p=0.000), have a higher mean albumin (37.4 versus 34.6 g/l for non-transplanted patients, p=0.000) and higher RRF (62.9 versus 52.4 l/wk/1.73m^2 for non-transplanted patients, p=0.001).

There is some variation among units in the proportion stopping PD as a result of transplantation which varies from 16.3% (unit 4) to 30.2 % (unit 7) (p=0.000). As expected, patients > 70 versus < 70 years are far less likely to be transplanted (0.8 versus 27.6%) (p=0.000). Patients with a BMI >30 kg/m^2 have a lower rate of transplantation than those with BMI <30 kg/m^2 (p=0.05). Patients with the lowest serum albumin concentrations (<30g/l) before the start of PD are significantly less likely to be transplanted than patients with higher serum albumin (8% versus 15.9% and 31% for serum albumin 30, 30-35 and >35 g/l respectively, p=0.000). Patients with no history of RRT or with previous HD only are more likely to stop PD for a transplant (24.7 and 19.0% respectively) than patients who had a transplant prior to PD (9.3%, p=0.02). There is no difference in deprivation categories or proportion of males between those who have been transplanted and those that have not.

Multivariate analysis with Transplantation as the Outcome

Most of these are entirely predictable factors reflecting the highly selective nature of transplant assessment and the listing of younger, fitter patients. On multivariate analysis using transplantation as the outcome (as the cause of stopping PD), younger age at starting

PD (for every 1 year increase in age HR 0.950, CI 0.932-0.968, p=0.000), higher serum albumin (per 1g/dl increase HR 1.05, CI 1.19-1.075), type of RRT before starting PD (with "no previous RRT" as the comparator group) those with previous transplant are less likely to stop PD for a further transplant (HR 0.333, CI 0.1222-0.905, p=0.031) (but for those with previous HD there was no significant difference).

10.4.6.2 Death

Detailed analysis of patient survival was presented in Chapter 9. In summary, on multivariate analysis the factors associated with risk of death (excluding transplanted patients) in our cohort were older age at start of PD (HR 1.05, CI 1.04-1.06, p=0.000), having DM (HR 1.40, CI 1.2-1.9, p=0.04), having primary GN (HR 0.57, CI 0.42-0.79, p=0.001), having interstitial nephropathy (HR 0.58, CI 0.42-0.79, p=0.000), serum albumin at start of PD (HR 0.96 for every g/l, CI 0.94-0.99, p=0.000) and RRF at start of PD (HR 0.995 for every 1/week/1.73 m^2, CI 0.993-0.998, p=0.000). However the survival chapter and analysis summarised above refers to patient survival regardless of whether the patient continues on PD or not. For the purposes of this chapter we are looking for predictors of patients dying *whilst still on PD*.

With respect to risk of dying on PD, previous RRT history is significant; 14% of those with previous transplant die on PD, 25.2% of those with previous HD die on PD, and 22.9% of those with no prior RRT die on PD (p=0.02) and patients with previous transplant have longer survival to death (median 3225 days, IQR1462-3225) than those with no previous RRT (median 2142 days, IQR1150-2774) and those with previous HD (median 1476 days, IQR 730-1666, p=0.000).

PRD is associated whereby only 13.1% of primary GN and interstitial nephropathy patients die on PD compared to 29.2-32.3% of patients with multisystem diseases, diabetic

nephropathy and unknown/other causes (p=0.000). Diabetics are more likely to die on PD (32.8%) than non-diabetics (19.9%, p=0.000) and have a shorter time to death on PD (median 1269 days, IQR 642-1965, versus non-diabetics (median 2482 days, IQR 1224-3225, p=0.000)

Lower BMI (<20 kg/m^2) is associated with higher risk of death on PD (34.6% versus 19.9-25% of other patients with higher BMIs (p=0.05)). Lower serum albumin is associated with higher risk of death on PD; 34.4% of patients with serum albumin <30g/l at the start of PD stop PD because of death versus 21.7% of those with serum albumin >30g/l (p=0.000) and a shorter time to death (median 1276 days IQR 704-2176 for serum albumin <30 g/l, versus 2342 days, IQR 1122-3225 for >30 g/l, p=0.000). Patients with <10 l/wk/1.73 m^2 RRF have shorter time to death than patients with >10 l/wk/1.73 m^2 (median 1462 days, IQR 618-2325 versus median 2342 days, IQR 1198-2774, p=0.000).

More recent PD eras have a lower proportion with death as the reason for stopping PD; 31.3% in *2000-2001*, 26.8% in *2003-2003*, 19.9% in *2004-2005* and 14.4% in *2006-2007* era (p=0.000) but no difference in time to death on Kaplan Meier analysis.

Multivariate Analysis with Death on PD as the Outcome

On multivariate analysis using death as the outcome (as the cause of stopping PD), older age at the start of PD carried a higher risk (for every year increased age, HR 1.058, CI 0.046-1.071, p=0.000), PRD (using "unknown/other" as the comparator group) primary GN (HR 0.554, CI 0.343-0.894, p=0.015) and interstitial nephropathies (HR 0.601, CI 0.385-0.939, p=0.025) have a lower risk of dying on PD, higher serum albumin associated with lower risk of death (for every 1g/l increase HR 0.946, CI 0.921-0.972, p=0.000), earlier PD eras (with 2006-2007 as comparator group) have higher risk of death 2000-2001 HR 2.214, CI 1.403-3.494 (p=0.001) and 2002-2003 HR 1.675, CI 1.067-2.630 (p=0.03)

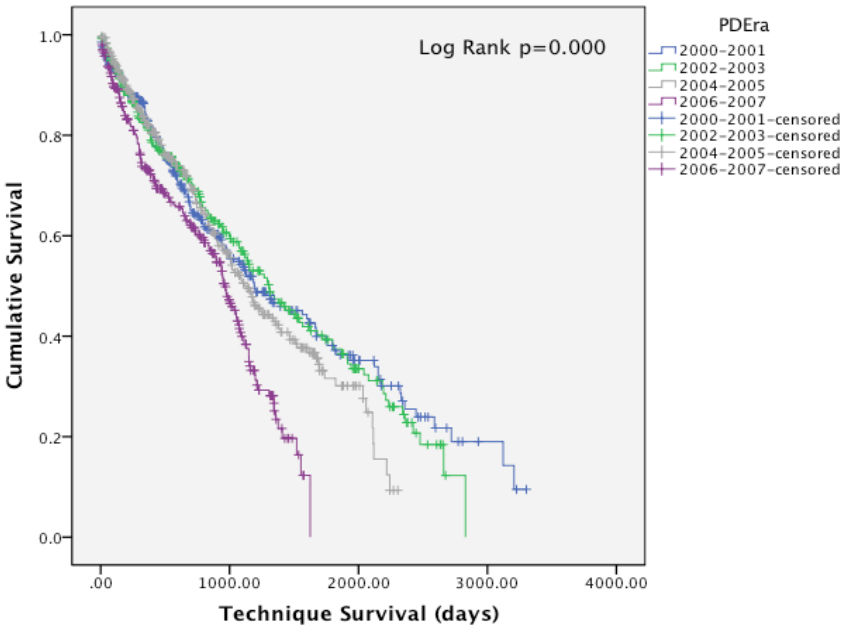
Technique Failure

As the number of episodes attributable to each cause of technique failure is variable and very small in some cases, the data are presented according to potential risk factor (or predictor) of technique failure. If there is a significant association with a specific cause of technique failure this is mentioned.

Gender. The only difference in cause of technique failure is higher likelihood of a fluid leak in females than males (4.7 versus 1.7%, p=0.04) but with small numbers (<20 cases) the significance of this is debatable. There is no difference in technique survival time.

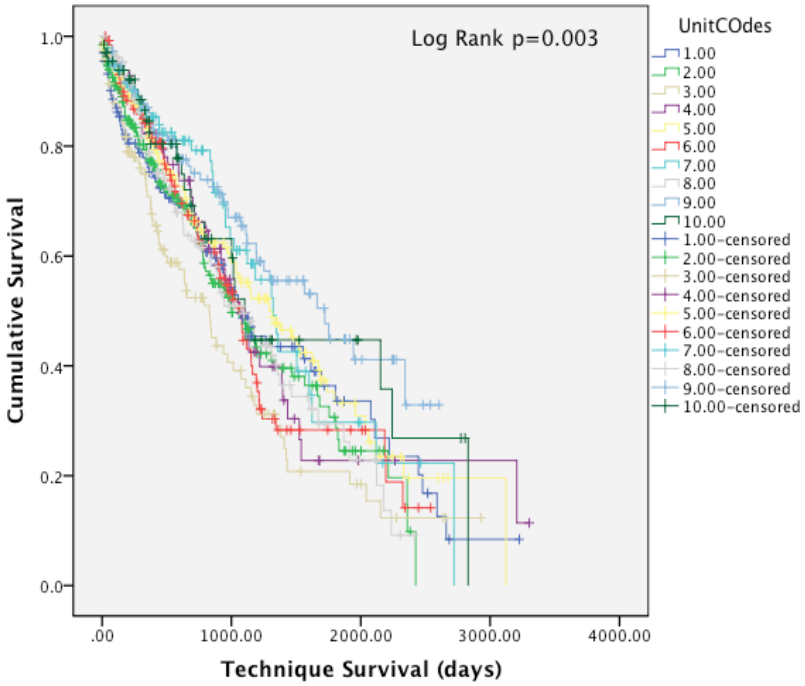
PD Era. Technique survival has become progressively shorter between the *2000-2001* and the *2006-2007* eras (figure 56). The median technique survival for each era are broadly comparable: *2000-2001* era 1193 days (IQR 533-2446), *2002-2003* era 1307 days (IQR 560-2343), *2004-2005* era 1134 days (IQR 562-2059 days), and *2006-2007* era 1113 days (IQR 482-1358). However, the interquartile range and survival plot show that the main difference in more recent eras is the technique survival beyond 3 years.

Figure 56. Kaplan Meier plot censored for transplantation, death and the end of the study period comparing technique survival according to PD era.



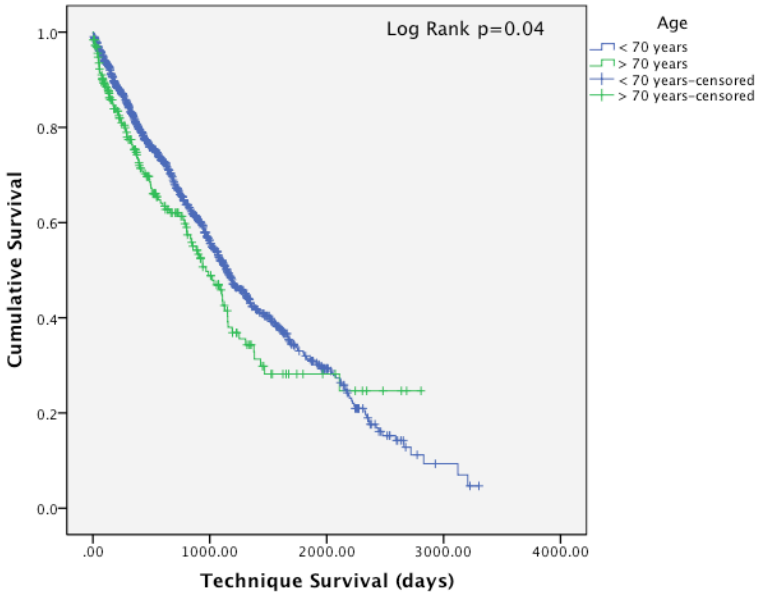
Unit. There is a significant difference between units in the median technique survival, varying from 830 days (IQR 307-1408) in unit 3 to 1723 days (IQR 760-2189) in unit 9 (p=0.003) (figure 56).

Figure 57. Technique survival by unit.



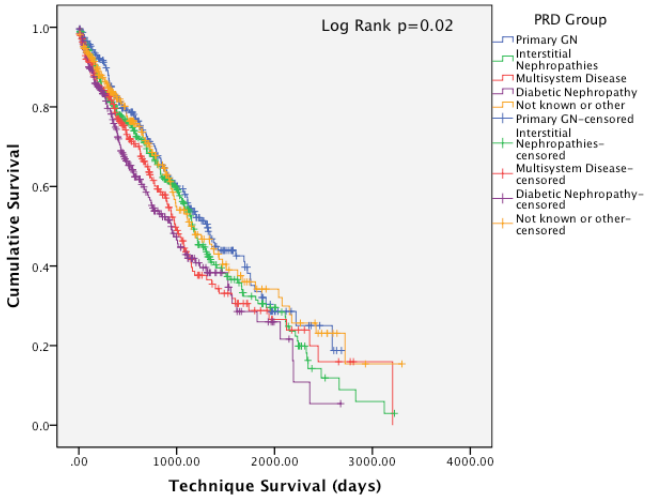
Age. The causes of technique failure for those <70 and >70 years old are similar. Elderly patients are more likely to stop because of patient choice (12.5 versus 6.4%, p=0.04) or social/physical problems (5.4 versus 2.0%, p=0.05). Elderly patients are less likely to stop PD because of inadequate dialysis than those < 70 years (11.6 versus 24.4%, p=0.003). Technique survival is shorter for older patients, but the survival curve suggests that beyond 3 years those >70 years may experience better technique survival (figure 58).

Figure 58. Kaplan Meier plot censored for transplantation, death and the end of the study period comparing technique survival for those < versus > 70 years old. (figure 58).



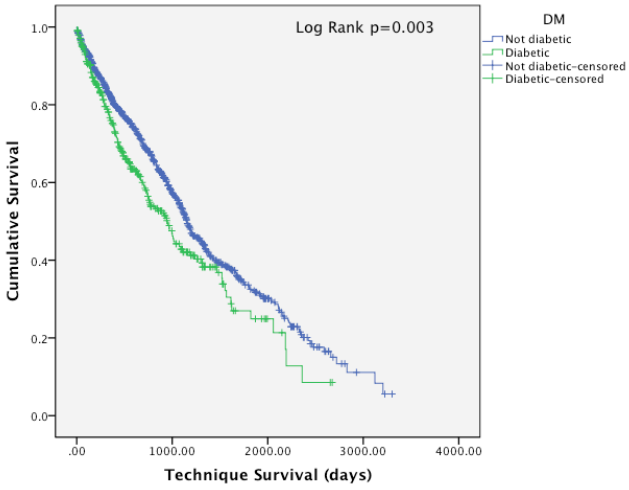
PRD. Across the 5 categories of PRD, there is no difference in the technique failure rate (46.1-52.0%, p=ns) or cause of technique failure. There is however a significant difference in technique survival time, with diabetics having the shortest (median 943, IQR 367-2059 days), multisystem disease next (982, IQR 472-2123 days), and the other three causes are almost superimposed upon one another (median technique survival: primary GN 1316, IQR 632-2590 days, interstitial nephropathies 1163, IQR 541-2118 days, unknown 1177, IQR 624-2424 days) (p=0.02) (figure 59).

Figure 59. Kaplan Meier plot censored for transplantation, death and the end of the study period comparing technique survival by cause of PRD.



Diabetes mellitus. Non-diabetics and diabetics have comparable rates and causes of technique failure. Diabetics have shorter technique survival, median 950 days (IQR 378-1822 days) versus non-diabetics median 1152 days (IQR 577-2212 days, p=0.003) (fig 60).

Figure 60. Kaplan Meier plot censored for transplantation, death and the end of the study period comparing technique survival for diabetic versus non-diabetics.



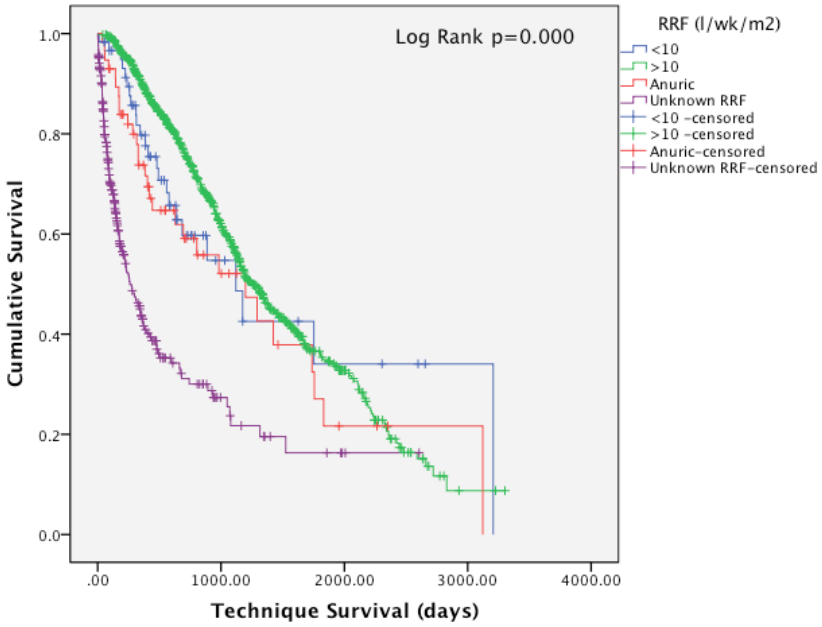
*Peritonitis***.** Not every case of peritonitis will result in technique failure, and patients may have multiple episodes of peritonitis in their PD careers. In our cohort, of those experiencing peritonitis at some point, more patients stop PD because of technique failure than those who avoided peritonitis (55.1 versus 39.3%, p= 0.0001) of which 63.2% have peritonitis listed as the ultimate cause of technique failure. There is no difference in technique survival time between those experiencing peritonitis and those who do not.

Residual Renal Function. Patients with lower RRF have shorter technique survival as shown in the Kaplan Meier plot (figure 61). The most significant difference is between those with RRF measurement and those without (p=0.000). If those with unknown RRF are excluded from the analysis, the difference between >10 l/wk/1.73 m^2/anurics and <10 l/wk/1.73 m^2 is just statistically significant (p=0.05).

As one would expect, the group with no RRF measurement had a much shorter median time on PD (260 days, IQR 84-1071) compared to those with >10 l/wk/1.73 m^2 (1251 days, IQR 730-2212), <10 l/wk/1.73 m^2 (1121 days, IQR 480-3207) and anuric patients (1198 days, IQR 315-1832) (p=0.000). In clinical practice those with RRF <10l/wk/1.73m^2 ("functionally anuric") and anuric patients are considered equivalent, as illustrated by our data. UF failure is more common in patients anuric at the start of PD compared to those with RRF (13.8% versus 5.8%, p=ns) but the numbers are small and in a bigger cohort this may reach statistical significance.

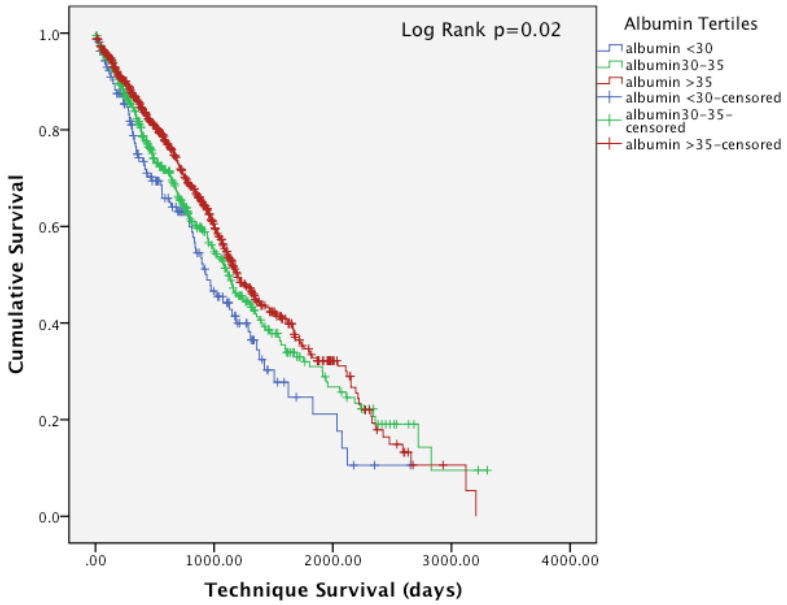
Those with unknown RRF are less likely to stop for inadequate dialysis (12.7 versus 20.8-25.4% for other groups, p=0.000) or peritonitis (33.3% versus 44.8-46.1% for other groups, p=0.01), and more likely to stop because of access issues (16.7% versus <4.2% for all other groups, p=0.02) or fluid leaks (7.3% versus <4.2% for all other groups, p=ns), in keeping with their lower PD exposure.

Figure 61. Kaplan Meier plot censored for transplantation, death and the end of the study period comparing technique survival according to RRF categories.



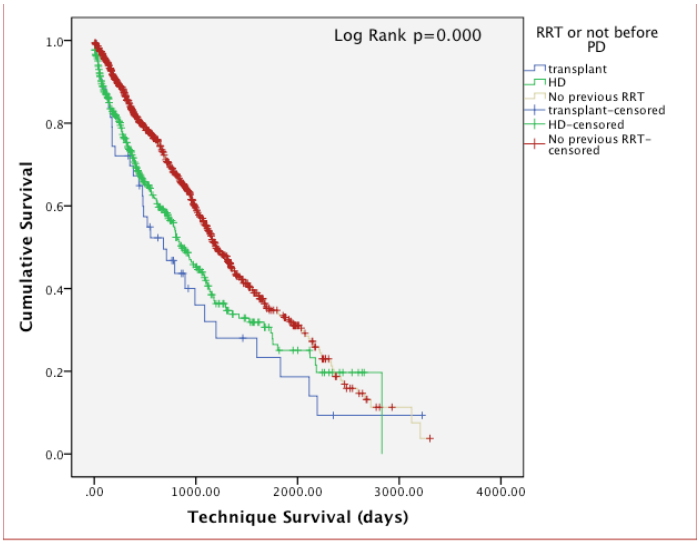
Serum Albumin. The causes of technique failure are broadly similar regardless of serum albumin but technique survival is significantly shorter for patients with lower serum albumin at the start of PD (Figure 62). Median survival for serum albumin <30 g/l is 939 days (IQR 343-1625), for 30-35 g/l median 1121 days (IQR 480-2114) and serum albumin >35 g/l 1198 days (IQR 660-2212), (p=0.02) showing that the major difference is between those with serum albumin <30 versus >30 g/l at the start

Figure 62. Kaplan Meier plot censored for transplantation, death, and the end of the study period comparing technique survival for tertiles of serum albumin.



*Previous RRT***.** Compared to patients who have had a transplant, patients with previous HD are less likely to transfer back to HD (47.3 versus 72.1%, p=ns). There is no difference in cause of technique failure between patients who have had previous RRT or not. There is a difference in technique survival between the groups with no history of RRT prior to PD versus those who had been transplanted or had previous HD (p=0.000) (figure 63).

Figure 63. Kaplan Meier plot censored for transplantation, death and the end of the study period comparing technique survival according to history of previous HD, transplant or neither.



BMI and Deprivation Categories. There is no difference in the causes of technique failure or survival across the spectrum of BMIs/deprivation categories.

Multivariate Analysis with Technique Failure as the Outcome

In summary, on univariate analysis the following factors are associated with shorter technique survival: PD unit (0.003), older age (p=0.04), diabetes mellitus (p=0.003), PD era (p=0.000), PRD (p=0.02), RRF (p=0.000), previous RRT (p=0.000) and serum albumin (p=0.02). On Cox regression analysis looking at technique survival, significant predictors of technique failure are: DM (HR 1.307, CI 1.038-1.646, p=0.02), lower RRF (HR 0.997 for every 1 l/week/1.73 m^2 increase in RRF, CI 0.995-1.0) and being in PD Era 2000-2001 compared to era 2004-2005 (HR 1.426, CI 1.087-1.87) and 2006-2007 (HR1.94, CI 1.45-2.61) (p=0.038).

10.4.7 What proportion of patients are still alive and on PD at 1, 2, 3, 4 and 5 years?

In order to summarise and present our data in a clinically useful format we have combined the outcome data, the proportion of patients who are still alive on PD overall and split by relevant groups in table 33 .The table highlights that few patients continue PD beyond 2 years because many have been transplanted, died or transferred to HD and a small minority have withdrawn from renal replacement therapy. Table 34 shows the reasons for stopping PD.

With respect to age, those <40 have a lower PD survival than those age 40-70 but this is explained by the higher transplant rate in this group. The main difference in PD survival is for the >70 year olds; 92.4% of those over 70 years old at the start of PD do not make it to 4 years of PD. Beyond 1 year, diabetics are much less likely to continue PD than non-diabetics with only 8.0% versus 15.5% making it to 4 years. Indeed, the likelihood of continuing PD for diabetics regardless of age is about the same as for >70 year olds. Table 34 below shows the reason for stopping PD for the patient groups, and it is apparent that about half of those >70 years stop PD because of transfer to HD and the other half die. Even though patients with primary GN and interstitial nephropathies are more likely to be transplanted, the remaining patients are also more likely to continue PD successfully.

From the tables 31 and 33 it is apparent that there are some differences between units, and that unit 9 appears to have better PD technique success as this unit has a greater proportion of patients continuing PD, less transferring to HD and still have greater numbers receiving transplants. Reasons for this are not clear but warrant further study. Patients with serum albumin <30g/l at the start of PD have consistently fewer patients continuing on PD beyond 1 year, and especially beyond 4 years (7.4%).

Table 33. Proportion of all patients and clinically relevant groups of patients on PD at 1,2,3,4 and 5 years after the start of PD.

Patient Group	Number and % of patients still on PD at given time point*				
	1 year	2 years	3 years	4 years	5 years
All patients (n=1324)[$]	868 (65.6)	563 (42.5)	333 (25.2)	179 (13.5)	99 (7.5)
Diabetic (n=348)	207 (59.5)	113 (32.5)	60 (17.2)	28 (8.0)	12 (3.4)
Non diabetic (n=976)	661 (67.7)	450 (46.1)	273 (28.0)	151 (15.5)	87 (8.9)
Age Group at start PD (years)					
≤40 (n=268)	171 (63.8)	106 (39.6)	64 (19.2)	40 (14.9)	20 (7.5)
>40-50 (n=227)	155 (68.3)	96 (42.3)	51 (22.5)	28 (12.3)	14 (6.2)
>50-60 (n=266)	199 (74.8)	135 (50.8)	83 (31.2)	44 (16.5)	27 (10.2)
>60-70 (n=313)	205 (65.5)	143 (54.7)	92 (29.4)	48 (15.3)	28 (8.9)
>70 (n=250)	138 (55.2)	83 (33.2)	43 (17.2)	19 (7.6)	10 (4.0)
PRD					
Primary GN (n=236)	172 (72.9)	120 (50.8)	82 (34.7)	43 (18.2)	22 (9.3)
CIN (n=350)	243 (69.4)	176 (50.3)	105 (30.0)	54 (15.4)	34 (9.7)
Multisystem disease (n=243)	153 (63.0)	89 (36.6)	46 (18.9)	28 (11.5)	15 (6.2)
Diabetic Nephropathy (n=269)	157 (58.4)	85 (31.6)	46 (17.1)	22 (8.2)	10 (3.7)
Unknown (n=226)	143 (63.3)	93 (41.2)	54 (23.9)	32 (14.2)	18 (8.0)
Unit[@]					
1 (n=133)	85 (63.9)	60 (45.1)	34 (25.6)	22 (16.5)	11 (8.3)
2 (n=246)	150 (61.0)	92 (37.4)	48 (19.5)	27 (11.0)	13 (5.3)
3 (n=118)	68 (57.6)	39 (33.1)	24 (20.3)	10 (8.5)	9 (7.6)
4 (n=86)	60 (69.8)	44 (51.2)	22 (25.6)	9 (10.5)	4 (4.7)
5 (n=201)	131 (65.2)	87 (43.3)	59 (29.4)	35 (17.4)	16 (8.0)
6 (n=133)	95 (71.4)	58 (43.6)	29 (21.8)	12 (9.0)	9 (6.8)
7 (n=96)	67 (69.8)	44 (45.8)	26 (27.1)	13 (13.5)	6 (6.3)
8 (n=131)	85 (64.9)	57 (43.5)	36 (27.5)	17 (13.0)	9 (6.9)
9 (n=112)	86 (76.8)	60 (53.6)	31 (36.6)	26 (23.2)	15 (13.4)
10 (n=68)	41 (60.3)	22 (32.4)	14 (20.6)	8 (11.8)	7 (10.3)
RRF (l/wk/1.73m^2)					
<10 l/week (n=117)	74 (63.2)	37 (31.6)	21 (17.9)	14 (12.0)	9 (7.7)
>10 l/week (n=918)	733 (79.8)	497 (54.1)	301 (32.8)	159 (17.3)	85 (9.3)
Unknown (n=289)	61 (21.1)	29 (10.0)	11 (3.8)	6 (2.1)	5 (1.7)
Serum Albumin (g/l)					
< 30 (n=163)	95 (58.3)	63 (38.7)	35 (21.5)	12 (7.4)	7 (4.3)
≥ 30-35 (n=390)	270 (69.2)	168 (43.1)	102 (26.2)	55 (14.1)	30 (7.7)
≥ 35 (n=603)	443 (73.5)	299 (49.6)	176 (29.2)	99 (16.4)	52 (8.6)

*Please note that as the patients on PD for e.g 3 years were also on PD at the end of 1 year and 2 years the row totals will not add up to the total number of patients given in the first column, and the total percentage does not add up to 100. The number of patients stopping PD before 1 year is not included as this information can be inferred from the number of patients *not on* PD at 1 year.

$ The 13 patients lost to follow-up have been included in the analysis for this table, and treated as if they stopped PD at the point they were lost to follow-up.

[@] The lowest and highest values are underlined in each column.

Table 34. Reasons for stopping PD according to clinically relevant subgroups.

	Reason for Stopping PD					
Baseline Status	**Transplant**	**Died**	**Transfer HD**	**Recovered**	**Withdrawn**	P value
Not Diabetic (n=934)	243 (24.9)	194 (19.9)	466 (47.7)	19 (1.9)	12 (1.2)	0.000
Diabetic (n=339)	55 (15.8)	114 (32.8)	160 (46.0)	3 (0.9)	7 (2.0)	
PRD						
Primary GN (n=225)	79 (33.5)	31 (13.1)	109 (46.2)	4 (1.7)	2 (0.8)	
Interstitial nephropathy (n=332)	96 (27.4)	46 (13.1)	182 (52.0)	5 (1.4)	3 (0.9)	
Multisystem Disease (n=236)	30 (12.3)	78 (32.1)	115 (47.3)	8 (3.3)	5 (2.1)	0.000
Diabetic Nephropathy (n=262)	46 (17.1)	87 (32.3)	124 (46.1)	2 (0.7)	3 (1.1)	
Unknown/other (n=218)	47 (20.8)	66 (29.2)	96 (42.5)	3 (1.3)	6 (2.7)	
Age < 70 years (n=1073)	296 (27.6)	191 (17.8)	515 (48%)	18 (1.7)	10 (0.9)	0.000
Age > 70 years (n=251)	2 (0.8)	117 (46.6)	111 (44.2)	4 (1.6)	9 (3.6)	
Serum Albumin (g/l)						
<30 (n=157)	13 (8.0)	56 (34.4)	81 (49.7)	2 (1.2)	5 (3.1)	
30-35 (n=375)	62 (15.9)	112 (28.7)	189 (48.5)	6 (1.5)	6 (1.5)	0.000
>35 (n=589)	187 (31.0)	103 (17.1)	278 (46.1)	12 (2.0)	12 (2.0)	
RRF (l/wk/m^2)						
<10 l/week (n=114)	20 (17.5)	38 (33.0)	53 (46.5)	1 (0.8)	2 (1.8)	
>10 l/week (n=886)	232 (25.3)	209 (22.8)	422 (46.0)	13 (1.4)	10 (1.1)	ns
Unknown (n=273)	46 (15.9)	61 (21.1)	151 (52.2)	8 (2.8)	7 (2.4)	

Note as 38 patients were still on PD and 13 had moved outwith Scotland, the total number of patients in each group may differ slightly from other tables for this reason.

10.5 Discussion

The aim of this study was to use the patient data for our incident PD cohort to analyse PD outcomes and examine the data for predictors of outcome. From a clinical perspective, knowing approximately how long one would expect a patient to continue, or survive, on PD would be helpful when planning ongoing management, such as the timing of referral to create an AV fistula for subsequent HD. From a patient's perspective such information may also be helpful, so that they are prepared for future changes in treatment.

PD Duration and Outcome in our Cohort

The most striking finding from our study of patient outcomes on PD is the limited duration of PD for the vast majority of patients. It is a short-term treatment in the Scottish population; with only 42.5 % of patients at 2 years and 25.2% of patients at 3 years still on PD. Technique failure is the leading cause (47.3%), followed by death (23.3%) and renal transplantation (22.5%) which is comparable to other countries (63, 258).

The duration of "PD survival" to each of these outcomes is comparable, with median duration of PD of 664 days (IQR 379-1164) before stopping for transplant, 541 days (203-1015) for transfer to HD and 564 days (243-1117) for death. We have a similar rate of early technique failure to other studies with <30% of all technique failures occurring by 6 months and 38.9% at 1 year in this study and 25% at 6 months and 44% at 1 year in a recent Canadian study (266). Both these studies report lower early technique failure rates than in a recent Swiss study (40% at 6 months) (268).

Our data show a difference in PD survival and outcome between units. In a PD population with similar demographics such differences between units are most likely to reflect differences in local practice. We cannot directly link outcomes to the size of the patient population per unit, but this has been shown to influence outcomes in other studies (63, 266, 269). It is interesting that there is a significant difference between 2 units which are <20 miles apart and have comparable patient populations (118 and 112 incident patients over the study period respectively, similar demographics) with median technique survival rates of 830 days (IQR 307-1408) in *unit 3* and 1723 days (IQR 760-2189) in *unit 9*. Such marked differences warrant further investigation to compare practice, but one cannot assume that longevity of PD therapy equates to best practice, or is in itself an appropriate target.

Whether some clinicians may persevere and try harder to adjust PD regimens to improve adequacy is impossible for us to measure retrospectively, and almost as difficult to gauge prospectively without an independent opinion. Physician factors, particularly male gender of the physician, have been shown to correlate with increased technique failure rates (266). The possible reasons for this are not clear, and the same study did not find clear association between physician experience and likelihood of technique failure.

The finding that in the most recent era (2006-2007) patients are significantly less likely to die on PD ($p<0.001$) would suggest that either the patients are younger/fitter now, but this is not supported by our data, or that patients are stopping PD sooner. With comparable proportions stopping for transplants, the main change is the increased numbers transferring to HD. Indeed the technique survival time has fallen in more recent eras in our cohort, in contrast to Guo et al's findings of improving technique survival over time (63). However, most of the improvement they reported was related to reduced infection related technique failure, and their study spanned a time of technique change (1999-2001) which may have improved the infectious complications, something we would not expect to see in our later study period.

When censored for death and transplantation, the median technique survival in our cohort is significantly shorter than in a recent Canadian study (n=5162) at 1113 days versus 2818 days but considerable longer than in Australia (657 days) and New Zealand (949 days) (74, 266). Although not stated in the paper, it appears that the Canadian survival analysis has not censored for death or transplantation that would explain at least part of the difference in survival time in their cohort (266). Arguably the Scottish PD population is more comparable to Australia in as much as our peritonitis rates are very similar (1 episode every 19.4 months in Australia versus 19.9 months in Scotland) and both are higher than in Canada (1 episode every 27.6 months) (23, 138, 217). Given that peritonitis may be the cause of more than 40% of all technique failures, the difference between technique survival in Canada and Scotland/Australia may be related to the differing peritonitis rates. The difference in technique survival between Australia and Scotland may relate to the higher rates of technique failure associated with peritonitis at 18% of episodes in Australia compared to 14% in Scotland.

If differences in technique survival are related to physician/PD nurse practices a greater proportion of technique failure may be attributed to inadequate dialysis in some units when loss of RRF with time on dialysis results in PD providing less adequate RRT. This appears to apply in unit 3 which has the highest (59.3%) technique failure rate, and has the highest proportion of technique failures (37.1%) attributed to inadequate dialysis. With increasing concerns about inferior patient survival on longer term PD (based upon the earlier HD:PD survival comparison studies) and the increasing risk of EPS with longer duration of PD exposure, some physicians may be less likely to persevere with PD in the current era than in the past? We do not know from this data whether clinicians/PD nurses have a lower threshold for stopping PD than they used to, but the falling numbers of PD patients and shorter duration of PD in the Scottish population compared to elsewhere would suggest a national trend that is *not* in favour of patients remaining on long-term PD.

Possible Predictors of Outcome

The univariate predictors of undergoing *transplantation* while on PD are self-evident, as they are the same markers associated with the selection criteria for transplantation listing; younger age, renal limited PRD, BMI <30kg/m^2 and higher serum albumin. However it is interesting that on multivariate analysis the only significant factors other than age are serum albumin (per 1g/dl increase HR 1.05, CI 1.19-1.075), and having had a previous transplant (HR 0.333, CI 0.1222-0.905, p=0.031). Other studies have shown diabetes, and female gender to be independently associated with increased likelihood of transplantation but this was not apparent in our data (63, 281, 282). The finding that patients with a previous transplant are *less likely* to stop PD for a further transplant (but much more likely to transfer to HD) could be explained by the greater likelihood of sensitisation and therefore longer wait for a suitable match, but our finding is in contrast with Guo et al who found no difference between patients who had started PD after a failed allograft and

patients new to RRT or who transferred from HD (63). Overall younger, fitter, slimmer patients with renal limited PRDs are more likely to receive a transplant, 70% of whom will do so before completing 3 years on PD.

With respect to the risk of *death*, most of the factors are predictable; age, PRD, and serum albumin. It is interesting that the proportion of patients dying on PD is lower in more recent eras, which may simply reflect the higher technique failure rate with patients being transferred from PD for whatever reason rather than continuing treatment to death. The finding that patients with the lowest serum albumin concentrations measured just before the start of PD are least likely to be transplanted and most likely to die on PD is not surprising; it simply reflects the reality that serum albumin is a marker of patient fitness.

Predictors of PD *technique failure* in our population included diabetes mellitus, lower RRF at the start of PD and being treated in the more recent eras. Overall the main causes of technique failure in our cohort are peritonitis (42.9%) and inadequate dialysis (22.1%), proportions which are very similar to other studies (63, 258). There was a higher proportion of technique failure due to peritonitis in this cohort than in the ANZDATA cohort (26%) (270). The small number of cases of the less common causes of technique failure prevents meaningful analysis of the risk factors of these causes.

The cause of technique failure varies by length of time on PD, as would be expected and the spread and timing of causes of technique failure in our cohort is comparable to previous studies (283). Access issues virtually all occur in the first 12 months of therapy, in keeping with data from the NECOSAD cohort (283). Interestingly half of patients who choose to stop PD, do so within the first year. Presumably this reflects the time in which most patients take to train, get used to the treatment and then decide it does not suit them.

Technique failure was higher among patients who had had a previous transplant compared to those transferred from HD or with no previous history of RRT. The reasons for this are not clear, although Guo et al found a trend toward the same finding (63).

The inconsistency in published studies with regard to the impact of age on technique survival is difficult to untangle (266, 270). Our data show that there is a shorter technique survival in elderly patients, but this is not a significant predictor when subjected to multivariate analysis. It is possible that patients and the clinicians caring for them have different thresholds for what constitutes adequate PD or acceptable PD related complications. For example, an elderly patient who is only achieving suboptimal combined clearance of 40 l/wk/m^2 but feels well and is able to maintain acceptable quality of life may be resistant to the idea of transferring to HD particularly if the clinician cannot guarantee that this will provide any quantifiable survival benefit. Such scenarios may explain the potentially "better" technique survival in elderly patients, but our data do not make it possible to examine this question.

10.5.1 How long can a patient expect to remain on PD in Scotland?

Assuming there are no significant changes in PD technique, only *a quarter* of PD patients can expect to undergo 3 or more years of PD. For diabetics, patients with multisystem disease, those >70 years old at the start of PD or patients starting PD with minimal RRF only around 17% will continue on PD for 3 or more years. Table 33 gives more detailed data on each clinically relevant patient subgroup to address the question of how long an incident patient may expect to remain on PD in Scotland.

10.5.2 Can we predict PD longevity?

In terms of whether we can predict outcome for a patient, there are some factors that make one outcome more likely, but it is not possible to accurately predict PD or technique survival on a patient-specific basis. We can however use our data to identify subgroups of patients who do well or badly. Again table 34 will give a broad indication as to expected PD duration in our population based on the likelihood of transplant, death or technique failure.

For those eligible to be listed for transplant PD duration will be influenced by likelihood and timing of transplant (e.g availability of living donor, previous sensitisation). With an average wait of 1100 days for a renal transplant, and a median technique survival 1149 days for <70 year olds, transplant listed patients have a good chance of ongoing PD technique success until transplantation.

For those not eligible for transplantation, it is more difficult to predict. On multivariate analysis hypoalbuminaemia, age >70 years, DM, low initial RRF and multisystem PRD are associated with either increased likelihood of death or technique failure. From our data only *a third* of patients with any of these "risk factors" will continue PD beyond 2 years, and only *about half* of those >70 years will continue PD beyond a year.

It is likely that there is also a cumulative effect of possessing more than one of these "risk factors" but the number of cases for subgroup analysis was too small to give meaningful results.

10.5.3 Potential Strategies to improve patient outcomes

The ideal improvement would be to increase the availability of kidneys for transplantation, something that is difficult to influence at unit level, beyond timely discussions about potential living donors. Modifying the risk of death is a huge subject of its own, but will include modification of cardiovascular risk, and avoiding infectious complications of PD.

Thereafter the focus is to try to modify the risk of technique failure, and therefore it is logical to try to prevent the individual causes as far as possible. Maximum effort to avoid peritonitis would be the most obvious target given its contribution to technique failure rates. Potential strategies in our population may include improved patient training/retraining or exit site prophylaxis (138, 284-286). There is some interest in the use of biocompatible fluids that may minimise progression of peritoneal changes and preserve peritoneal function (287). Recent observational data support previous evidence that icodextrin improves technique (HR 0.6) and patient (HR 0.69) survival (280). It is not clear whether the improved technique survival is entirely attributable to better ultrafiltration, as icodextrin has previously been shown to improve fluid balance status, or its greater biocompatibility and more favourable metabolic impact (288-291). Use of ACE/ARB drugs to preserve the peritoneum may help, but further studies are required (189, 265).

The consistent finding that a low serum albumin is a risk factor for peritonitis, reduced likelihood of transplantation, reduced patient survival and reduced technique survival would make it an obvious target to modify, if it was modifiable. As discussed in previous chapters, serum albumin may be a marker of malnutrition, and potentially amenable to dietary supplementation, or relate to intercurrent illness, which may or may not be treatable. Regardless of the potential cause there is currently no clear evidence that attempting to improve serum albumin impacts upon patient outcomes.

Another area whereby PD technique may be prolonged is by employing assisted PD which has been associated with improved technique survival (292). In our cohort 18 (1.4%) patients stopped PD for social or physical reasons and another 47 (3.5%) patients stopped PD by their own choice. These patients were unlikely to have been given the option of assisted PD as it was not available in Scotland until the very end of the study period, and is still not widely used. It is reasonable to assume that some of these patients may have opted to continue PD if assistance was offered to them, and it will be interesting to see the extent of assisted PD usage in our population now that it has become established.

10.5.4 Limitations

Although the study was analysed retrospectively all the data was gathered prospectively and was near complete. We did not have details of PD prescriptions, type of dialysis fluid used, daily UF volumes, serial RRF measurements to assess rate of loss of RRF and did not attempt analysis of modality of PD (APD versus CAPD) on patient outcomes.

10.6 Conclusion

The majority of patients starting PD in Scotland can expect to continue on PD for less than 2 years, regardless of whether they receive a transplant, die or experience technique failure. It is apparent that older age, hypoalbuminaemia, diabetes mellitus, or having a multisystem primary renal diagnosis predict poorer outcome to varying degrees in terms of lower chance of transplant, higher risk of death or greater likelihood of technique failure. The influence of PD unit and falling technique survival in more recent eras raises the question of whether changing attitudes to PD and varying clinical practice may be one of the major determinants of technique success in Scotland. This question warrants further investigation. The findings of our study may be used to help guide patient management and inform patients of the likelihood of PD longevity in Scotland.

Chapter 11

Conclusion

12. Conclusion

One of the initial motivations for carrying out this study was the concern about EPS and the question as to whether our PD practice should alter in view of this potential complication. The reality is that PD usage was already falling through the 1990s and continues its inexorable decline year on year. The most likely reason for this in Scotland, and throughout most of the developed world, would appear to relate to nephrologists' practice; PD studies, and the large PD populations in some units would suggest that far more patients could be maintained on PD than currently are. Whether we should be trying to increase or put limits on PD practice was a major clinical question we hoped our study may help clarify. Before considering the impact our results may have in relation to this question, it is worth examining whether previous evidence supports the decline of PD in favour of HD.

It is possible that clinicians in Scotland are more familiar with the older studies that suggested a survival benefit for HD, and therefore feel patients will have better outcomes on HD (34). This belief is not supported by numerous more recent comparative studies of patient survival on PD versus HD. These suggest that either the modalities are equivalent, or PD may offer a survival benefit in the first 2 years, and perhaps HD a survival benefit beyond 2 years (35, 39, 40, 42). Our data show that only 42.5% of the Scottish PD population continues PD to 2 years, and just 25% to 3 years. Current survival studies cannot therefore be used as justification for not commencing PD, given that the vast majority of PD patients will stop PD just beyond 2 years. The only potential exception may be diabetics (especially older diabetic females), who may fare better on HD but there is insufficient data to state that they should not be offered PD and more studies are required (35, 228).

In terms of patient satisfaction with treatment, PD patients have been shown to be more content than HD patients, and the obvious advantages of home dialysis therapy would support greater use of PD (86). Elderly patients who are unable to perform PD and lack home support will have been justifiably excluded from PD in the past. With an increasingly elderly RRT population this may be affecting the relative proportions on different RRT modalities. Assisted PD programmes successfully support a largely elderly PD population in France, at a lower cost than HD even with private nurses providing the assistance (88). Units are beginning to offer assisted PD in Scotland, and one could argue that if their ability to provide assistance to patients who would otherwise be excluded from PD, we should be offering this option routinely, expanding the service as required.

It appears that PD has become less popular without good evidence to provoke this change. As PD numbers dwindle, staff expertise decreases and creates a vicious circle. It was in this context that we began examining the Scottish PD population, initially motivated by the local concerns about EPS risk.

Whether we should be pushing to expand PD numbers, with the potential risk of EPS is a major consideration. Our study has confirmed the devastating nature of EPS with a 46.8% mortality at 1 year. The comparison of survival with PD population is falsely reassuring, as it does not compare like with like. The survival plot (chapter 6, figure 31) demonstrating the significantly better survival of the EPS patients until the EPS was diagnosed illustrates this. The people who are developing EPS are amongst the fittest PD patients, as they have been able to survive on PD long enough to get it.

We could not identify any clear risk factors for EPS except for PD duration, with an exponential rise in incidence with increased PD exposure. Given that this is a modifiable risk factor, nephrologists are keen to establish if and when they should stop PD.

The major risk of EPS is beyond 4 years. Given that only 25% of patients manage to continue PD to 3 years, and only 13.5% at 4 years, the proportion being exposed to a significant risk of EPS is actually very small. The cumulative risk graph (chapter 7, figure 34) takes this in to consideration by displaying the absolute incidence based on everyone who has been exposed to PD and plotting the proportion who ultimately end up with EPS, only censoring at death. By 5 years only around 2% of all patients who started PD have developed EPS, reflecting the fact that most patients will have stopped PD long before being at risk. This analysis could allow clinicians to roughly quantify the overall risk of EPS when starting a patient on PD, whilst incorporating the uncertainty of transplantation, technique survival and death. When the same graph is plotted but censored for technique failure, death and transplantation, it is apparent that the cumulative risk of EPS for those continuing PD beyond 5 years is alarmingly high, but the numbers of patients very small (chapter 8, figure 35). This graph, or the data in chapter 8 table 21, may be more relevant once patients have been on PD for a period to assess the risk of ongoing therapy.

In absolute numbers the risk of EPS is very small for the vast majority of our patients. However, in the same manner that we consent patients for procedures and are required to quote important risks, even if very low, the high mortality associated with EPS should at least prompt clinicians to formally discuss this with patients (293). Whether this discussion happens at the start, which we feel it should given that EPS can occur earlier, or at a set time point such as 3 or 4 years should be for the clinician to decide pending formal guidelines to direct management.

It is interesting that despite our colleagues' concerns about EPS and prolonged PD exposure, there is no evidence that they have modified their practice; the proportion of patients on PD > 4 or 5 years is the same in 2011 as in 1999. This means that the falling prevalent PD population cannot be attributed to clinician-driven limiting of PD exposure.

Based upon our evidence that most patients have their PD exposure limited by death, transplantation or technique failure, there is no need to consciously limit PD exposure most of the time if we wish to avoid EPS. Using our data it would be justifiable to formally review ongoing PD for those whom the technique continues successfully. The timing must be assessed individually, and risk:benefit analysis considered. For an elderly patient whose predicted survival is much the same as it would be with EPS, and is otherwise succeeding on PD it may be reasonable to continue after counselling him or her about the risk of EPS.

Our patient outcome data show that the patients most likely to have ongoing technique success are also those most likely to survive and most likely to be listed for a transplant; younger patients, those with renal-limited PRDs and greater RRF. If these patients are not transplanted by 4 years, they will become the patients most likely to get EPS by virtue of surviving long enough on PD. They also have the best overall survival, and arguably the most to lose with EPS. For a young, otherwise healthy patient with ongoing technique success at 3 years who is on the transplant list, EPS would be a disaster. We feel these are patients for whom limiting PD would be justified, at least while there are no reliable screening tests or treatments for EPS. Between 3-4 years the EPS risk is around 1 in 25, and beyond 4-5 years 1 in 13. Timely discussions about stopping PD and referral for vascular access would seem appropriate around 3 years to avoid the highest risk exposure.

Over the study period the EPS incidence figures changed as the incident cohort experienced longer PD exposure. The exponential rise in EPS incidence with time is clear, and the importance of accurate incidence calculation and adequate, defined follow-up is highlighted by our re-analysis at several time points. We are confident we have established an accurate risk of EPS in our patient population, but are mindful that while the cause of EPS in unknown, and PD practice changes EPS rates may change and we must continue to monitor this condition.

With respect to the risk of EPS, our data would *not* support restricting specific patients from commencing PD in the first place, given that the majority will stop PD before being at significant risk of this disease. However, whether specific patient groups do particularly badly or well on PD was another question we were interested in.

When looking at the outcomes or complications of PD, we observed several patient factors that were consistently associated with poorer outcomes namely increased peritonitis rate or reduced peritonitis-free survival, reduced technique survival, and reduced patient survival. Hypoalbuminaemia (serum albumin<30g/l), increasing age (particularly >70 years), lower RRF at the outset of PD, DM, and multisystem causes of PRD were all associated with poorer outcomes to some extent or another.

With respect to age, this is a non-modifiable factor, and a characteristic that brings specific considerations. For a start, the elderly are unlikely to be listed for transplant and therefore PD or HD are required for survival. The patients may carry greater comorbidity in which case survival is likely to be limited, and technique survival may be less of an issue. Even if the RRT technique continues successfully, risks such as EPS may be relatively insignificant given the lower predicted patient survival for elderly patients, and adequacy targets less important. Quality of life and minimising travel to, or time in hospital may be the priority more so than for a younger patient. These are generalisations, but important considerations. Striving to prolong life is not always the most important factor for a patient and this is particularly so for an elderly patient for whom we cannot guarantee RRT will achieve in whatever form. Avoiding hospitalisation is important for all patients, and therefore avoiding peritonitis is preferable. However, the organisms responsible for the greater peritonitis burden in the elderly are mainly gram negative and therefore less preventable.

Hypoalbuminaemia is a consistent "risk factor" for complications and poor outcomes in our cohort. It is associated with shorter peritonitis-free survival (HR 0.98 CI 0.96-0.99, p=0.005), increased risk of gram negative peritonitis (p=0.008), relapse of peritonitis (p=0.01), risk of death on PD (HR 0.946, CI 0.921-0.972, p=0.000), patient survival in general (HR 0.96, CI 0.94-0.99, p=0.000) lower chance of transplantation (HR1.05, CI 1.19-1.075, p=0.001) and shorter technique survival (p=0.02). In the various chapters the possible causes of hypoalbuminaemia, potential strategies to improve it and debate as to whether intervening will alter outcomes have been discussed. In short there currently is no evidence that attempting to improve serum albumin will impact upon patient outcomes. However, intuitively it seems appropriate to actively seek and treat the likely cause if possible. For example, identifying a source of chronic inflammation such as recurrent urine infection or chronic undernutrition and treating as appropriate.

It is intriguing that hypoalbuminaemia is such a consistent marker for poor outcome, particularly when it is based upon a single reading taken before PD has started and therefore cannot reflect the impact that PD itself may have on a patient's protein losses or nutritional state. It seems likely that many clinicians will attribute a low serum albumin prior to starting PD as reflecting uraemia and not realise the powerful predictor that it appears to be in our population. As with other potential predictors of poor outcome there is not enough evidence to tell us that patients with low serum albumins do better on HD, or should not be offered PD. However, as part of a whole patient assessment, finding a low serum albumin should be noted, and may be helpful when trying to predict PD longevity. Further, detailed studies are required to examine the role of serum albumin and its interrelationship with PD protein losses, urinary protein losses, patient nutritional status and overall health. Until these studies help clarify the pathophysiology, hypoalbuminaemia can only be seen as a marker of poor outcome rather than a modifiable risk factor.

Lower residual renal function is also associated with poorer outcomes in our population. This is not a surprise with respect to patient survival as this is well described in the literature (24). It also impacts upon technique survival, which is what we would expect. However a similar proportion of patients who were anuric (RRF <10l/wk/1.73 m^2) at their first adequacy test had ongoing technique success to the average PD population (12.5 versus 13.5% at 4 years, shown in chapter 9). This would serve as an argument for not using poor RRF as a contraindication to PD as these patients can experience significant technique survival. We did not examine serial adequacy results, and it is possible that patients may have seen a degree of recovery of RRF after the first adequacy test, but as the question is whether it is worth continuing PD once anuria is recognised, and our data would suggest yes. No reason to modify care because of this.

DM and cause of PRD are non-modifiable factors, and the poorer patient survival in these groups and absence of convincing data that HD would offer superior outcomes, would support the ongoing use of PD in these patients if they wish it. Duration of PD is likely to be limited (only 30% at 2 years, 17-19% at 3 years for DM and multisystem PRD groups) and therefore concerns about EPS, possible lower survival on PD versus HD will be relevant to a small proportion of patients. Unless these patients are transplanted their survival will be poor on whatever modality they are on. Trying to avoid infection for diabetics, especially peritonitis is worthwhile to reduce mortality, improve technique survival and reduce hospitalisation.

Even if clinicians are wary of ongoing PD, there are more reasons to prioritising technique survival than just to prolong PD treatment. In practice prolonging technique survival will mean avoiding the major causes; peritonitis and inadequate dialysis. Options to reduce peritonitis in our population would be routine exit site prophylaxis and formal retraining programmes for patients.

Avoiding inadequate dialysis should mainly involve attempting to preserve RRF, using ACE/ARB, avoiding dehydration and nephrotoxins. These strategies may allow PD to continue, but as peritonitis and lower RRF are themselves risk factors for poor outcome in general, it is in the patients best interests to avoid even if planned transfer to HD.

Preserving RRF should be a priority regardless of whether the intention is to continue on PD or HD. It predicts patient survival. Our analysis of adequacy results in our population show that those with ≥30 l/wk/1.73 m^2 RRF will always achieve current UK Renal Association adequacy targets (>50 l/wk/1.73 m^2) potentially obviating the need for concomitant PD clearance measurement. Clearly the PD prescription should be tailored to the individual patient, and as discussed in Chapter 6, adequate dialysis incorporates more than just solute clearance; for example patients who are symptomatic of uraemia, suffer from fluid retention, or labile blood pressure may require more close adjustment of PD prescriptions(87). Some patients may require less PD and thus have lower PD clearances. Therefore the assumption that all patients will achieve a minimum clearance as described in our cohort is a generalisation. However, there is no convincing evidence that increasing the peritoneal contribution to total adequacy improves patient outcomes. This may change with ongoing study, but currently we would argue that routine measurement of peritoneal clearance wastes resources that may be better spent on means of preserving RRF. This may mean routine prescribing or ACE/ARB drugs, specific PD fluids or at least more frequent RRF measurement such that PD prescriptions can be modified as soon as RRF falls (15).

Our data can only be used to identify patient groups, or patient characteristics associated with poorer outcome. We cannot use this to conclude that these patients should not be offered PD, as we do not have evidence that the same patients would do better on HD.

Similarly, even if some patient groups are unlikely to survive more than 1-2 years on PD, these years may preserve the patient's vascular access for this period, or are at very least allow time to establish reliable vascular access rather than resort to tunnelled central venous catheters (TCVCs). We envisage that the data will help guide clinicians when planning patient care, particularly when considering transferring patients to HD. The data will also be helpful when discussing RRT with patients and preparing them for the future; if we inform an elderly diabetic lady that she is very unlikely to be on PD after 2 years then it will not be a shock if she cannot continue beyond this time.

We must keep in mind that our data for patient outcomes may be skewed by current nephrologists' attitude and practice. The larger proportion of RRT patients on PD in unit 9, combined with their lower peritonitis rates and longer technique survival would suggest that practice is influencing outcomes. Technique survival may be shortened if clinicians have a lower threshold for stopping PD. If they are then reassured by survival studies and our data regarding the risk of EPS, they may be more inclined to persevere with PD and potentially produce improved technique survival.

We feel that based on the basis of recent published data and our own assessment of the current Scottish PD population, PD should be offered to all patients who do not have a contraindication. How hard we try to initiate PD, for example sending a patient for hernia repair simply to facilitate PD, may be guided by the likelihood of that patient continuing reasonable time on PD. With the falling PD population, steps need to be taken before PD dwindles further and potentially is no longer available as an option for our patients.

In order to reverse the trend there is a need to ensure nephrology trainees gain sufficient PD experience to feel confident counselling patients about this modality pre-dialysis, and to deal with complications among established PD patients. Offering assisted PD has been

shown to increase PD uptake and prevalence and would be a logical and economically sound step particularly for elderly patients (77). There is a strong argument for offering this routinely as the very patients who are excluded from PD are often those for whom survival may be limited, transporting to and from dialysis an expensive effort and quality of life a priority. Allowing these patients to dialyse at home could dramatically alter their quality of life and the demographic of the HD units.

Arguably there should be further efforts to encouraging daily home haemodialysis in the younger fitter patients, but this is a subject unto its own, beyond the scope of this thesis and the routine practice of current Scottish units.

In the interim there may need to be a culture shift to making more effort to establish elderly, less able patients on PD whilst consciously limiting PD duration in the young fit patients to reduce the EPS risk.

Appendix 1

Scottish Renal Registry Codes for Scottish Renal Units

1	Aberdeen Royal Infirmary
2	Western Infirmary Glasgow
3	Royal Infirmary Glasgow
4	Queen Margaret Hospital Dunfermline
5	Royal Infirmary Edinburgh
6	Ninewells Hospital Dundee
7	Monklands Hospital Airdrie
8	Raigmore Hospital Inverness
9	Crosshouse Hospital Kilmarnock
10	Dumfries and Galloway Royal Infirmary

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