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Recent peritonitis associates with mortality among patients treated with peritoneal dialysis

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Recent peritonitis associates with mortality among patients treated with peritoneal dialysis

Abstract
Peritonitis is a major complication of peritoneal dialysis, but the relationship between peritonitis and mortality among these patients is not well understood. In this case-crossover study, we included the 1316 patients who received peritoneal dialysis in Australia and New Zealand from May 2004 through December 2009 and either died on peritoneal dialysis or within 30 days of transfer to hemodialysis. Each patient served as his or her own control. The mean age was 70 years, and the mean time receiving peritoneal dialysis was 3 years. In total, there were 1446 reported episodes of peritonitis with 27% of patients having ≥2 episodes. Compared with the rest of the year, there were significantly increased odds of peritonitis during the 120 days before death, although themagnitude of this association wasmuch greater during the 30 days before death. Compared with a 30-day window 6 months before death, the odds for peritonitis was six-fold higher during the 30 days immediately before death (odds ratio, 6.2; 95% confidence interval, 4.4–8.7). In conclusion, peritonitis significantly associates with mortality in peritoneal dialysis patients. The increased odds extend up to 120 days after an episode of peritonitis but themagnitude is greater during the initial 30 days.

Keywords
dialysis, peritonitis, peritoneal, recent, treated, patients, among, mortality, associates

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Title: Recent peritonitis associates with mortality among patients treated with peritoneal dialysis**.**

Running Title: PD peritonitis and mortality

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Abstract:

Patients on peritoneal dialysis have a high annual mortality rate. Peritonitis is also a major complication of peritoneal dialysis but the association between peritonitis and mortality has not been examined systematically. Our aim was to determine the relationship between peritonitis and mortality in patients on peritoneal dialysis. This was a case-crossover study where individual patients served as their own control. All people receiving peritoneal dialysis in Australia and New Zealand between 1st May 2004 and 31st December 2009 and died on peritoneal dialysis, or within 30 days of transfer to hemodialysis, were included. 1316 patients were included with a mean age of 70.4±11.7 years and receiving peritoneal dialysis for 2.9±2.0 years. 1446 episodes of peritonitis were reported with 27% of patients having 2 or more episodes. A significantly increased odds of peritonitis prior to death compared with the rest of the year was seen up to 120 days before death, although the magnitude of this association was much greater in the immediate 30 days before death. The odds ratio of peritonitis in the 30 days prior to death compared to a 30 day window 6 months prior to death was 6.2 (95% confidence interval 4.4, 8.7). In conclusion, peritonitis was significantly associated with mortality in peritoneal dialysis patients. This increased odds extended up to 120 days following an episode of peritonitis but the magnitude is greater in the initial 30 days and it may be that the latter is the preferred new definition of peritonitis-associated mortality.

Introduction:

Annual mortality for peritoneal dialysis (PD) patients is between 10 and 20%. [1] Infectious causes of death account for a variable proportion of deaths on PD, 5.9 to 33%, depending upon the publication examined and the population studied.[1-3] The majority of these infections in PD patients are due to peritonitis, with rates varying between centres. It is difficult though to ascertain the definition of infection-, in particular peritonitis-, associated death as often it is a clinical diagnosis without any clearly defined criteria.

The evidence that peritonitis increases a patient's risk of death is primarily descriptive in nature or extrapolated from peritonitis outcomes in non-dialysis patients.[4-5] There has been limited statistical analysis formally examining the relationship between peritonitis and death, primarily related to the brevity and intermittent nature of the at-risk period.[6] The patient that has peritonitis and is septic then dies, clearly has a likely causal relationship between the two. However, the inflammatory state that an infection creates within an individual may also predispose to vascular events, especially in those with pre-existing disease, possibly leading to cardiovascular or cerebrovascular death.[7-9] These events may even occur a period of time after an infection.[10]

Our aim was to explore the relationship between mortality and peritonitis in PD patients by determining whether peritonitis was more likely to occur in the time immediately before death than in periods distant to death. We utilise a case-crossover design to compare the likelihood of peritonitis at different times, where individual patients serve as their own control.[11]

Results:

There were 1316 PD patients who died while receiving PD treatment (or within 30 days of transfer to hemodialysis) included in the analyses, 44% of whom were female. Patients mean age at death was 70.4±11.7 years, with a mean time on PD of 2.9±2.0 years (Table 1). Patients were predominantly Caucasian (78%), with 10.7% Asians and 8.9% Aboriginal or Torres Strait Islanders (ATSI). A total of 1446 peritonitis episodes were documented, with 56% experiencing ≥1 episode, and 27% ≥2. Mortality was attributed to peritonitis in 6% of deaths. The median (25th and 75th percentile) time between peritonitis episode and death was 247 days (64-552) (Figure 1).

Of the 250 patients with an episode of peritonitis in the 30 days prior to death, 69 (27.6%) had peritonitis as the stated cause of death. For the remaining patients the cause of death was categorised as cardiac (68, 27.2%), withdrawal (40, 16%), non-peritoneal infection (20, 8%), cerebrovascular (13, 5.2%), malignancy (7, 2.8%), peripheral vascular events (5, 2%), and other causes (28, 11.2% including bowel infarction, gastrointestinal haemorrhage, cachexia and abdominal perforation).

Determination of the duration of the 'window' period

In order to ascertain the preferred duration of the window to be used in this analysis, 5- and 7- day windows were used at intervals prior to death and the occurrence of peritonitis during that window was compared to all of the preceding periods up to 12 months before death (Figure 2a and 2b). The odds of peritonitis in any 5 day period more than 30 days prior to death were no different than any other early period in the year before death (Figure 2a).

However, patients were more than 2.5-times more likely to have peritonitis in the window 30 days before death (95% confidence interval (CI)=1.7-3.6, P<0.001) than during any earlier period and the odds ratio increased to 4.1 times in the 5-days immediately before death (95%CI=3.2-5.3 p<0.001). A similar pattern was observed using 7-day windows, with the risk of peritonitis significantly increased from 28 days to 7 days immediately before death (odds ratio (OR) range 2.9-5.7). Since there were statistically significant odds ratios for both 5 and 7 day windows until 30 days prior to death, 30 days was utilised as the duration of the windows to examine the association between mortality and peritonitis.

Potential at risk period of the association between peritonitis and mortality

Upon utilising a 30 day window at different intervals before death and comparing the incidence of peritonitis with all other 30 day windows in the 12 months prior to death, there was a significantly increased odds of peritonitis up to 120 days prior to death but the magnitude of this association was much greater in the first 30 days (OR=6.5, 95%CI=5.4-7.7, P<0.001) (Figure 2c).

Magnitude of the odds of peritonitis prior to death

In the 30 days immediately prior to death, 250 (19.0%) patients experienced an episode of peritonitis, compared to 88 (6.7%) in the 30 days 6 months before death. The OR of peritonitis in the 30 days prior to death compared to a 30 day window 6 months prior to death was statistically significant at 6.2 (95%CI = 4.4, 8.7) (Table 2). Similar statistically significant associations were seen when the comparator period was 3 and 9 months prior to death.

Association of peritonitis and cause of death specific mortality

A significantly increased odds of peritonitis in the 30 days prior to death was detected in patients who died from cardiovascular, cerebrovascular or peripheral vascular disease (OR=3.4, 95%CI=2.4, 4.6) (Figure 3a). Similar findings were detected in patients who died from infectious causes and those that were coded as having withdrawn from dialysis (Figure 3b and c).

Sensitivity analysis

Sensitivity analysis of the 30 day window demonstrated that there was no significant difference in the odds ratio of peritonitis at varying time periods prior to death more remote than the period immediately prior to death (Table 3). This was consistent when only PD patients with one episode of peritonitis were included.

Demographic and clinical predictors of peritonitis in the 30 days prior to death

Peritonitis in the 30 days prior to death was significantly associated with history of coronary artery disease, time spent on peritoneal dialysis and the number of peritonitis episodes they had previously. The odds ratio of peritonitis in the 30 days before death increased by 1.07 for each additional year spent on PD (95%CI=1.00-1.15, P=0.049), and by 1.70 for each additional case of peritonitis (95%CI=1.55-1.89, P<0.001). However, patients with a history of coronary artery disease were less likely to have peritonitis in the 30 days prior to death compared with those without this comorbidity (OR=0.71, (95%CI=0.51-0.99, P=0.048). (Table 4).

Discussion:

Patients on PD have an annual mortality rate of 10-20%.[1] In Australia and New Zealand, 15% of PD patients that died were coded as having done so due to infections, with approximately 6% due to peritonitis.[1] In fact, 19% of PD patients died with peritonitis occurring in the preceding 30 days. We have demonstrated that in those patients that died on PD there was an approximately 6-fold increase in the odds of peritonitis in the 30 days before death compared to the 30-day period 6 months prior to death.

There is currently no standard definition of peritonitis-associated mortality. Not surprisingly therefore, there is appreciable variation in the reported prevalence of peritonitis-associated mortality in the literature, ranging from 5.9% up to 33% of deaths.[2-3, 12] Although a proportion of this variability reflects differences in case-mix and racial origins, coding differences are also likely to contribute.

In many cases, the diagnosis of peritonitis-associated death is made by the treating physician and is somewhat subjective. Some physicians may only diagnose peritonitis-associated mortality in cases where the patient presented with systemic manifestations of sepsis and immediately died, while others include all deaths following a period of time after an episode of peritonitis. For example, a previous series of publications from the ANZDATA Registry defined peritonitis-associated mortality as “death directly attributable to peritonitis in the clinical opinion of the treating nephrologist”.[13-21] In contrast, Perez-Fontan et al defined peritonitis-associated mortality as death “a) during the course of a clinically active peritonitis, or b) during the week following complete clinical, bacteriologic, and cytological remission of

an episode of peritonitis, or c) in the case of a refractory peritonitis demanding catheter removal, before hospital discharge for reinitiation of regular dialysis therapy (PD or HD)".[22] Alternatively, Szeto et al defined peritonitis-associated mortality as "death from any cause during antibiotic treatment (generally 2 to 3 weeks, depending upon the organism) or death during temporary hemodialysis (generally four weeks after catheter removal)".[23]

It is difficult to define the length of the at-risk period following peritonitis. It may be that the risk of mortality is elevated only during the couple of weeks of active inflammation or it may extend past this point. These variable and subjective approaches to diagnosing peritonitis-associated death make it exceedingly difficult to compare, contrast and explore observed differences in peritonitis-associated death rates between different centres, regions and countries. Our results would make a case for diagnosing peritonitis-associated death as any death within 30 days of an episode of peritonitis. Our finding of significantly greater odds of peritonitis in the period just prior to death was consistent using different periods of time distant from death. The sensitivity analysis confirmed that this finding was not related to increased peritonitis risk with time on dialysis.

Most studies that have examined factors that may influence patient survival in PD populations have failed to include peritonitis as an independent variable.[2, 24-25] Sipahioglu et al, in their single centre retrospective study of 423 PD patients, demonstrated that for every increase in peritonitis rate by one episode per 12 patient months there was an associated 1.87 fold increased relative risk of mortality.[6] This was performed by entering the peritonitis rates into a Cox proportional hazards model which may not be appropriate as these models are not well suited to intermittent exposures with time-varying effects.[26] This approach would also

have difficulties in selecting an appropriate control group (i.e. patients who did not die on PD). These patients are likely to be fundamentally different from those who die on PD and this approach may introduce control-selection biases.

We chose to use a case-crossover design. This method is used to determine the relationship between an intermittent exposure and an outcome.[27-28] A case-crossover study differs from a case-control study in that all participants are cases (i.e. all have experienced the outcome), all have had the opportunity to be exposed and unexposed at different study periods, because the risk posed by the exposure is transient. Rather than having case and control patients, the case-crossover design uses case and control periods of time to determine whether the exposure occurs more often in the 'case' period, immediately before the event, than in the 'control' period/s, more distant to the outcome.[27] Therefore, the case-crossover design assesses the *timing* of the exposure relative to the outcome, using participants as their own controls.

The advantage of this design is that it examines the association between time-varying exposures on an outcome while controlling for constant patient-level confounders and avoiding control-selection bias.[29] The main limitations of case-crossover studies are that they do not account for within-person (time-varying) confounders, or account for the role of chronic exposures.[27] The design we used ensured that stable patient factors such as age, ethnicity and baseline co-morbidity were controlled for, however the design did not account for patient factors which may have changed rapidly, such as nutritional status, anaemia, or volume status.

We selected this design given that PD patients may be repeatedly exposed and unexposed to peritonitis during their treatment, and that the risk of mortality posed by peritonitis is

unknown but it would be reasonable to assume that if an increased risk exists it is likely to be time-limited. The case-crossover design allowed us to determine whether peritonitis was more likely to occur in the period immediately before death for PD patients than during earlier periods. A recent paper used this methodology to identify eight potential trigger factors immediately prior to the rupture of intracranial aneurysms in 250 patients.[30] Similarly, mobile phones were demonstrated to be associated with motor vehicle accidents using this technique .[31]

The finding in the present investigation of an increased risk of death for up to 120 days following an episode of peritonitis may be potentially explained by a persistent systemic inflammatory state, which may predispose them to cardiovascular events.[7-9, 32] This inflammatory state may lead to cardiovascular or cerebrovascular events that are remote to the time of the peritonitis.[7-9] Our finding that there is a significant association between peritonitis and death from vascular disease is supportive of this hypothesis. There are other possible mechanisms explaining why peritonitis may be associated with increased mortality, including through its effects on increased frailty, requirement for medications, possible hospitalisation, and adverse effects on nutritional status.[33] A further exploration is required into our documented association between peritonitis and death reported as Withdrawal. This may be mislabelling by the Registry and a better understanding of the reasons for withdrawal may provide additional insight into this association.

The strengths of this study include its large sample size and inclusiveness. We included all patients in Australia during the study period that died whilst on PD, or within 30 days of transferring to haemodialysis, this greatly enhanced the external validity of our findings. In addition, the study methodology reduces the potential for confounding and accounts for the

nature of the exposure. These strengths should be balanced against the study's limitations, the principal ones being that those patients sick enough to die may also be more likely to develop peritonitis, and that we could not adjust for rapidly-changing patient factors. Our study does not prove a causal link between peritonitis and mortality. In common with other Registries, ANZDATA is a voluntary Registry and there is no external audit of data accuracy, including the diagnosis of peritonitis and cause of death. Consequently, the possibility of coding/classification bias cannot be excluded. It is also possible that physicians report peritonitis events more often when they occur in close proximity to death. The study design also will not correct for any potential time-varying confounders. As the data for this study is obtained from a single region, and limited to those patients that had been on PD for a minimum of 7 months, the results may not necessarily be generalizable to other PD populations.

In conclusion, we have established for the first time that there is a significant association between mortality and peritonitis. We recommend that a new definition of peritonitis-associated mortality be made that includes any death within 30 days following an episode of peritonitis to reduce the chances of mislabelling.

Concise methods:

All patients on the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry that died on PD or within 30 days of transferring from PD to hemodialysis, between 1st May 2004 and 31st December 2009 were included in this study. Patients also had to be on PD for a minimum of 7 months to allow a control period of time, distant to the time of death, to compare the peritonitis rates with. Ethics approval was received from The University of Western Australia.

The start date for peritonitis was defined as the date of diagnosis, based upon clinical features of peritonitis (abdominal pain or cloudy dialysate) and dialysate leukocytosis (white blood cell count > 100 /μL with > 50% neutrophils).[34] Variables collected from the ANZDATA Registry included dates of all diagnosis of peritonitis, patient demographic characteristics (ie. age at time of death, gender, race, geographic remoteness at commencement of dialysis) and clinical characteristics (ie. body mass index (BMI), cause of primary renal disease, co-morbidities at the start of dialysis, smoking status, Kt/V, membrane transport characteristics and cause of death). These data are collected by nursing and medical staff in each renal unit in Australia and New Zealand and are submitted to the ANZDATA Registry annually.

Statistical analysis

We used a time-stratified case-crossover design whereby each patient acted as his or her own control (Figure 4).[11, 35] Two sampling periods were determined – i) the 'case' window, immediately prior to the patient's death, and ii) a 'control' window, of equal duration, distant from the time of death. We varied the duration of these windows and the distance from the

time of death in our analyses. Conditional logistic regression was used to compare the odds of peritonitis in the 'case' window compared with the 'control' window for the same patient. This method eliminated the influence of stable patient-level confounders, such as sex, race and comorbidities. This method was used to assess the association between peritonitis and all-cause mortality, death due to vascular disease (defined as death due to cardiovascular, cerebrovacular or peripheral vascular disease), death due to infection and death due to withdrawal of dialysis. Cause of death was defined by the treating physician.

Peritonitis may be more likely to occur the longer a patient is on dialysis, so a sensitivity analysis was performed examining the relative risk of peritonitis in two 30 day windows that are both distant from the time of death, including 6, 9 and 12 months. Another sensitivity analysis was performed examining patients with one episode separately to patients with multiple episodes of peritonitis.

Logistic regression was used to determine the patient demographic and clinical characteristics predictive of peritonitis in the 30 days before death. Univariate models were initially used to examine the relationship between each variable and peritonitis within 30-days of death. The categorical variables examined were sex, age group (<60, 60-74, ≥75), state of residence, Aboriginal or Torres Strait Islander status, BMI category (underweight <20, healthy 20-24.9, overweight 25-29.9, obese ≥30), smoking status (current, former or never), membrane transport status category (low <0.50, low average 0.50-0.64, high average 0.65-0.80, high ≥0.81), and comorbid diabetes, chronic lung disease, coronary heart disease, peripheral vascular disease, and cerebrovascular disease (yes/no). The continuous variables examined were time on PD (years) and number of peritonitis episodes. The linearity assumption was tested by examining the interaction between these variables and their log transformations, and

was not violated in either case.[36] Those variables significantly predicting peritonitis within 30 days of death ($p < 0.05$) were included in a multivariate logistic regression model (coronary heart disease, time on PD and number of peritonitis episodes).

Conditional logistic regression analyses were conducted in SAS version 9.2. All other statistical procedures were conducted in IBM SPSS Statistics version 19.

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Statement of competing financial interest

Associate Professor Neil Boudville has previously received research funds from Roche, travel grants from Roche, Amgen and Jansen Cilag, and speaking honoraria from Roche.

Dr Wai Lim is on the Advisory Board for Novartis, Genzyme, Bristol Myer Squibb and Pfizer, he has also received research grants from Novartis, Genzyme and Pfizer, plus speaking honoraria from Novartis and Genzyme.

Professor David Johnson is a consultant for Baxter Healthcare Pty Ltd and Fresenius Medical Care and has previously received research funds from Baxter. He has also received speakers' honoraria and research grants from Fresenius Medical Care and Baxter.

Dr Kym Bannister is a consultant for Baxter Healthcare Pty Ltd, on their Clinical Advisory Board and received speaking honoraria.

Dr Fiona Brown is a consultant for Baxter and Fresenius and has received travel grants from Amgen and Roche.

Dr Stephen McDonald has received speaking honoraria from AMGEN Australia, Fresenius Australia and Solvay Pharmaceuticals and travel grants from AMGEN Australia, Genzyme Australia and Jansen-Cilag.

The remaining authors have no competing financial interests to declare.

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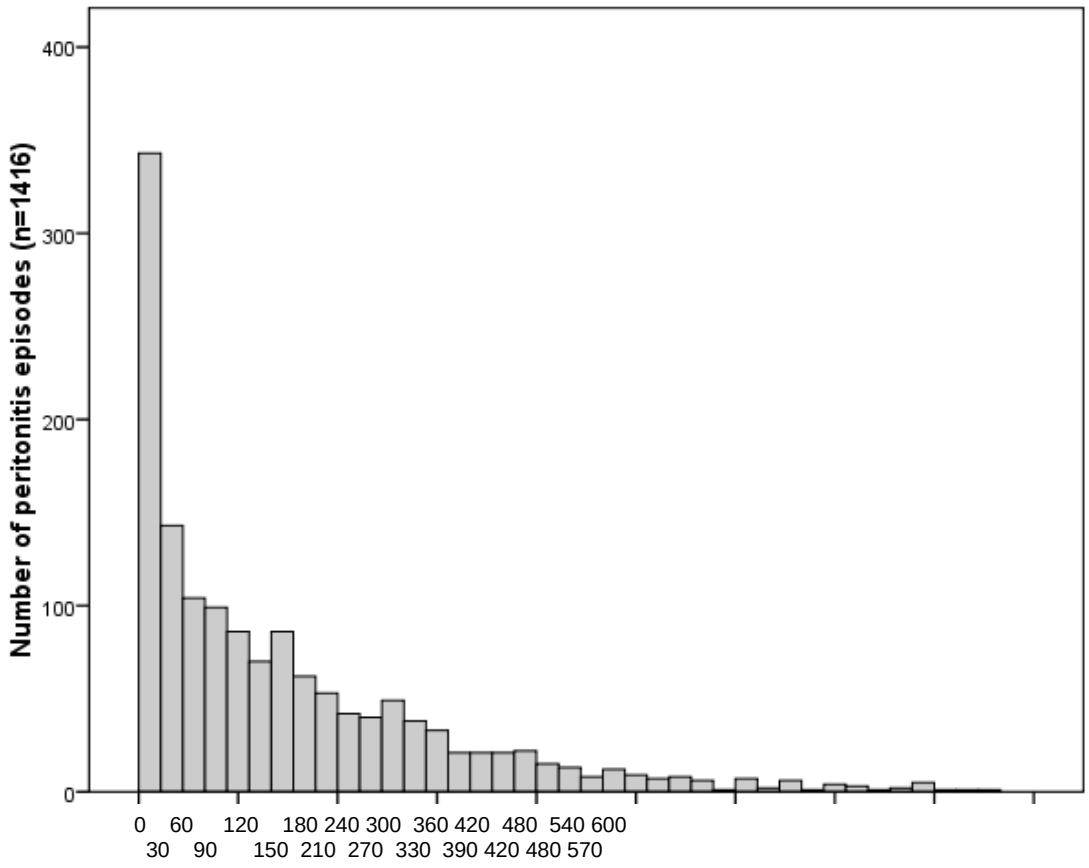

Figure 1: Days between peritonitis episode and death.

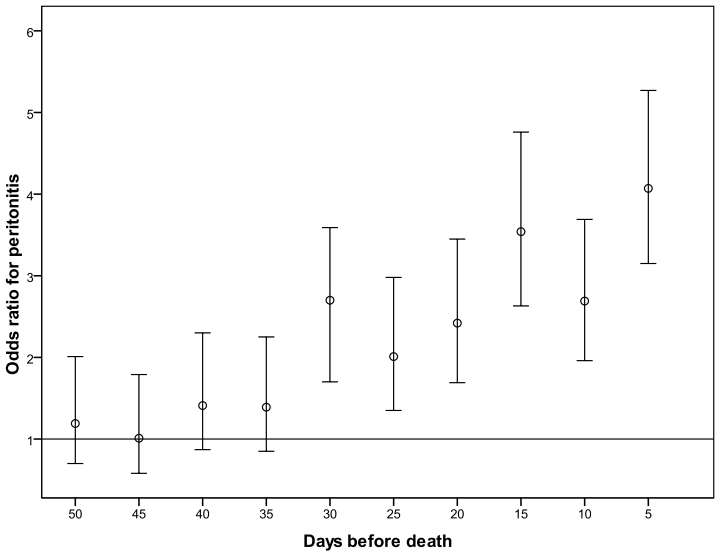

Figure 2a: Odds of peritonitis in different 5-day periods prior to death compared with all other preceding 5-day periods in the year before death.

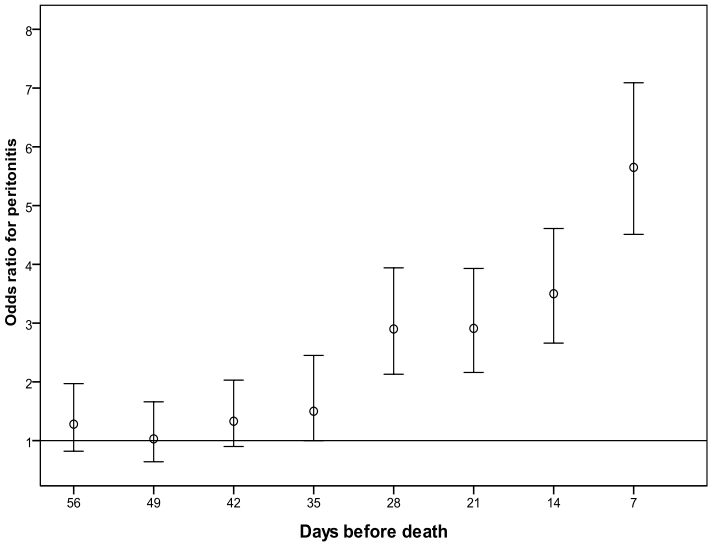

Figure 2b: Odds of peritonitis in different 7-day periods prior to death compared with all other preceding 7-day periods in the year before death.

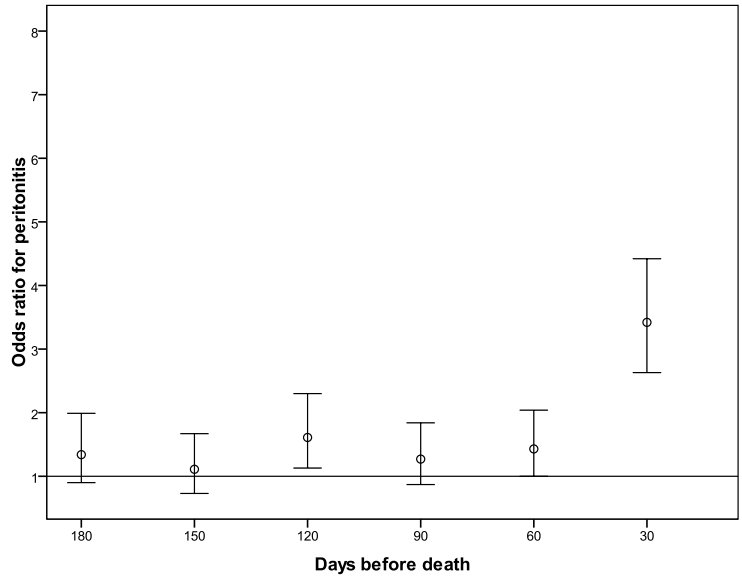

Figure 3 a. Odds of peritonitis in different 30-day periods prior to death from vascular disease compared with all other preceding 30-day periods in the year before death. (n= 733)

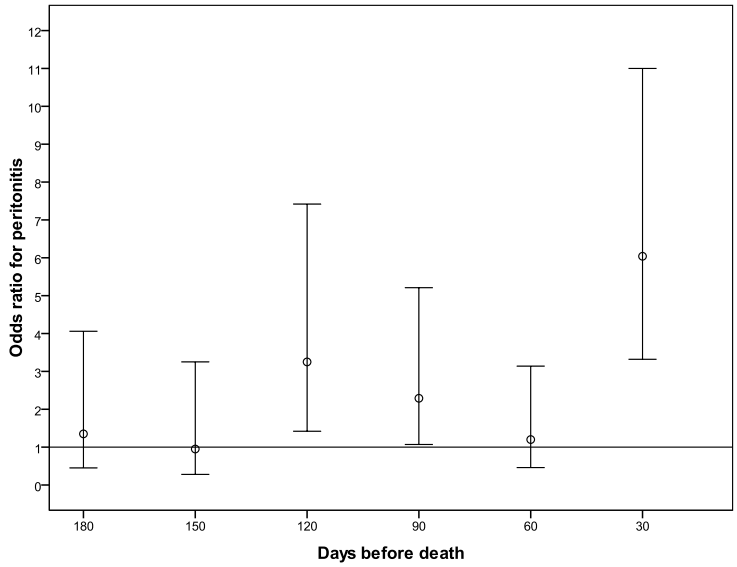

Figure 3 b. Odds of peritonitis in different 30-day periods prior to death from Infection compared with all other preceding 30-day periods in the year before death. (n=115)

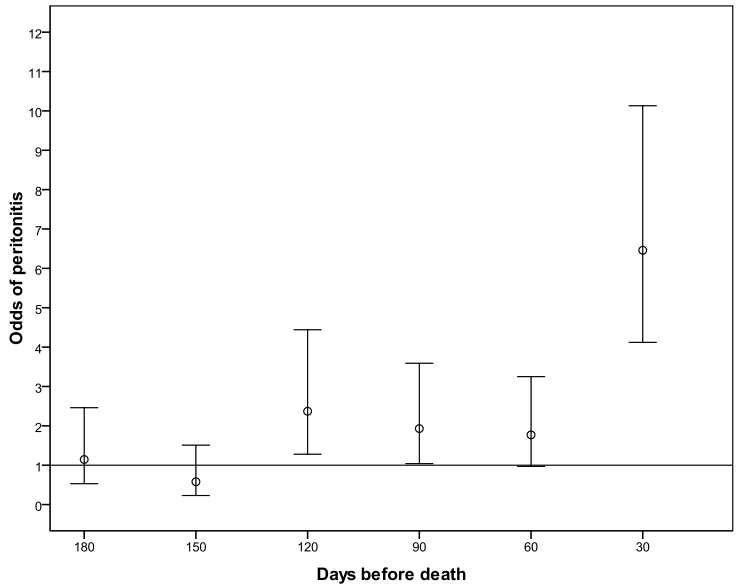

Figure 3 c. Odds of peritonitis in different 30-day periods prior to death from Withdrawal from dialysis compared with all other preceding 30-day periods in the year before death. (n=174)

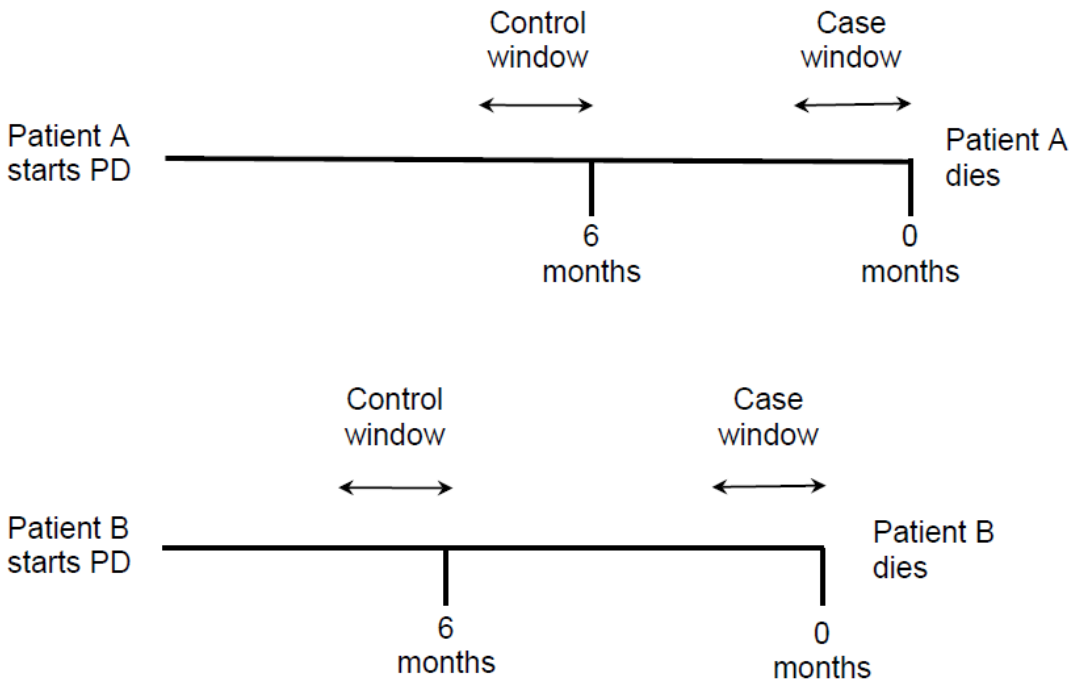

Figure 4. Case-crossover method in which individual patients serve as their own control. The odds of peritonitis occurring within the case window (period immediately before death), which can be of varying lengths, is compared to a control window (period remote from death, in this figure 6 months prior) of equal duration.

N	1316
Female	582 (44.2%)
Age at start of Peritoneal Dialysis (PD) (years)	67.5 (11.8) [#]
Age at death (years)	70.4 (11.7) [#]
Time on PD (years)	2.3 (1.4-3.9)*
State of residence:	
New South Wales & Australian Capital	556 (42.2%)
Territory	234 (17.8%)
Victoria	125 (9.5%)
Western Australia	271 (20.6%)
Queensland	21 (1.6%)
Tasmania	88 (6.7%)
South Australia	21 (1.6%)
Northern Territory	
Region of residence:	
Major city	720 (54.7%)
Regional	345 (26.2%)
Remote	69 (5.3%)
Unknown	182 (13.8%)

Ethnicity:	
Caucasian	1023 (77.8%)
Asian	141 (10.7%)
Pacific	34 (2.6%)
Aboriginal and Torres Strait Islander	117 (8.9%)
Cause of death:	
Peritonitis	78 (5.9%)
Other infection	115 (8.7%)
Cardiac	578 (43.9%)
Cerebrovascular	107 (8.1%)
Peripheral vascular	48 (3.6%)
Malignancy	96 (7.3%)
Withdrawal	174 (13.2%)
Other	120 (9.1%)
Number of peritonitis episodes:	
None	584 (44.4%)
One	380 (28.9%)
Two	170 (12.9%)
Three or more	182 (13.8%)
Median days from peritonitis to death	247 (64-552)*

Smoking status	
Current	145 (11.0%)
Former	581 (44.1%)
Never	590 (44.8%)
Body Mass Index (kg/m^2):	
<20	106 (8.1%)
20.0-24.9	456 (34.9%)
25.0-29.9	472 (36.1%)
≥30	273 (20.9%)
Diabetes:	
Type I	53 (4.0%)
Type II non-insulin requiring	330 (25.1%)
Type II insulin requiring	312 (23.7%)
Other comorbidities:	
Chronic Lung Disease	369 (28.0%)
Coronary Artery Disease	1029 (78.2%)
Peripheral Vascular Disease	710 (54.4%)
Cerebrovascular Disease	508 (38.6%)
No comorbidity	78 (5.9%)

Membrane transport status	
Low	52 (4.0%)
Low average	327 (24.8%)
High average	479 (36.4%)
High	191 (14.5%)
Unknown	267 (20.3%)
Kt/V (total)	1.8 (0.6) [#]

Table 1: Cohort demographic and clinical characteristics.

[#] mean (standard deviation)

*25th and 75th percentile

Table 2: Odds ratio of peritonitis in the 30-days prior to death compared to the 30-day period 3, 6 and 9 months prior to death (with 95% confidence intervals).

Comparator month	**Odds ratio**	**95% confidence intervals**
All patients		
3 months [a]	4.07	3.04-5.45
6 months [a]	6.23	4.44-8.74
9 months [b]	6.97	4.84-10.04
Patients with 1 episode		
3 months [c]	8.36	4.80-14.55
6 months [c]	5.09	3.25-7.95
9 months [d]	11.10	5.81-21.20

a:n=1316

b:n=1221

c:n=380

d:n=359

Table 3: Sensitivity analysis comparing the odds ratio of peritonitis in a 30-day window at two different periods of time prior to death

	Odds ratio	**95% confidence intervals**
All patients		
6 months versus 9 months [a]	0.95	0.64-1.48
6 months versus 12 months [b]	0.81	0.51-1.27
Patients with 1 episode		
6 months versus 9 months [c]	1.10	0.47-2.59
6 months versus 12 months [d]	0.91	0.39-2.14

a:n=1221

b:n=1120

c:n=359

d:n=328

Table 4: Results from logistic regression showing odds of peritonitis in the 30-days prior to death for selected patient demographic and clinical characteristics[a].

	Odds ratio	**95% confidence intervals**	**P-value**
History of coronary artery disease	0.71	0.51-0.99	0.048
Time on peritoneal dialysis (years)[b]	1.07	1.00-1.15	0.049
Number of peritonitis cases[b]	1.71	1.55-1.89	<0.001

a: N = 1316.

b: Odds ratios refer to each unit increase.