Higher serum C-reactive protein predicts short and long-term outcomes in peritoneal dialysis-associated peritonitis

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We examined the association between C-reactive protein (CRP) and short- and long-term adverse outcomes in peritoneal dialysis (PD)-associated peritonitis. Serum CRP levels were measured at baseline and 3 weeks after initiation of treatment in 209 patients with an incident episode of peritonitis between 1 January 1999 and 31 March 2005. Patients were followed until 31 May 2005. Short-term adverse outcomes included switch to hemodialysis, death, persistent infection beyond planned therapy duration, and relapse; long-term adverse outcomes included a subsequent peritonitis event or death. After adjustment for age, gender, diabetes, duration of renal replacement therapy and causative organism, patients with higher CRP levels at diagnosis had a greater odds of an adverse short-term outcome (odds ratio 1.57 (95% confidence interval (CI): 0.61–4.02), 2.73 (95% CI: 1.09–6.87), and 3.38 (95% CI: 1.36–8.42) in the second, third, and highest quartiles). In patients who met criteria for resolution of peritonitis 3 weeks after diagnosis, those with higher CRP levels had a greater risk of a long-term adverse outcome (hazard ratio 1.79 (95% CI: 1.05–3.07)). In conclusion, higher levels of CRP are independently associated with adverse outcomes in PD-associated peritonitis. Serial measurement of this marker during the course of peritonitis may facilitate earlier identification of individuals at greater risk of complications.

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Peritonitis is an important cause of morbidity, mortality and technique failure in peritoneal dialysis (PD) patients.[1] Patients generally remain ambulatory during the treatment of peritonitis and contact with medical personnel may be relatively infrequent. For these reasons, easily obtainable predictors of short- and long-term outcomes would be clinically useful. Previous studies have identified several factors associated with adverse outcomes from peritonitis, including causative organism, duration of dialysis, and prolonged elevation of PD fluid white blood cell count (WCC) after initiation of antibiotic treatment.[2,3] However, neither causative organism nor persistence of elevated PD fluid WCC is available at the time of diagnosis. Furthermore, many patients have culture negative infections.

C-reactive protein (CRP) is a marker of inflammation, and elevated serum levels have been associated with an increased risk of cardiovascular events and mortality in the general population as well as in patients with kidney disease.[4–12] The potential utility of serial CRP measurements in predicting outcomes from PD-associated peritonitis was initially reported in a series of 39 consecutive patients.[13] In this study, the magnitude of the CRP response correlated with the severity of the episode, patients who resolved with antibiotics showed a prompt fall in CRP towards normal, and patients in whom the serum CRP value remained raised had a complicated course; however, the association between CRP and hard end points, such as mortality and recurrent peritonitis events, has not been examined.

The purpose of this prospective cohort study was to examine the association between CRP levels and outcomes from PD-associated peritonitis in patients presenting with an incident episode of peritonitis. Specifically, our objectives were (1) to determine if CRP level at the time of diagnosis is associated with an increased risk of adverse outcomes in the short term, including switch to hemodialysis owing to peritonitis, death during the course of treatment, persistent infection after completion of intended antibiotic treatment, or relapse of peritonitis; and (2) in the subgroup of patients whose peritonitis is clinically resolved 3 weeks following

initiation of treatment, to determine whether CRP level is associated with an increased risk of long-term adverse outcomes, including development of a subsequent peritonitis event or death from any cause.

RESULTS

Study patient characteristics

During the study period, 228 PD patients had an incident episode of peritonitis; 19 patients with missing data for the baseline CRP level were excluded. Demographic characteristics of the 209 included patients and the organisms cultured from the dialysate at presentation are shown in Table 1. The majority of infections were caused by Gram-positive organisms (53.1%), followed by Gram-negative organisms (19.6%), and culture negative infections (17.2%). In all, 10% of patients grew more than one organism from the initial PD fluid specimen. Patients with missing baseline CRP values had similar demographic characteristics to the remaining subjects (data not shown).

Table 1 | Baseline demographic characteristics of the study population

	Incident patients N=209
Age (year) (mean ± s.d.)	58.9 ± 16.9
Male (*n*, %)	123 (58.9)
Cause of ESRD (n, %)	
Diabetes	40 (19.1)
Glomerulonephritis	41 (19.6)
Other	128 (61.2)
Diabetes (*n*, %)	65 (31.1)
Cardiovascular disease (*n*, %)	95 (45.5)
Duration of RRT (year) (median, 25–75th percentile)	1.0 (0.3–2.3)
Duration of PD (year) (median, 25–75th percentile)	0.8 (0.2–1.6)
PD system (n, %)	
CAPD	162 (77.5)
APD	47 (22.5)
Baseline (mean ± s.d.)	
Hemoglobin (g/dl)	10.6 ± 1.8
White blood cell count	11.2 ± 5.3
Albumin (g/l)	32.4 ± 5.7
Fluid culture at baseline	
Gram positive (*n*, %)	111 (53.1)
Coagulase-negative *Staphylococcus*	70
Staphylococcus aureus	18
Streptococcus species	16
Diphtheroids	4
Enterococcus	3
Gram negative	41 (19.6)
'Coliforms'	3
Escherichia coli	17
Klebsiella	6
Pseudomonas	6
Enterobacter	2
Acintetobacter	2
Bacteroides	2
Prevotella	1
Pasteurella	1
Neisseria	1
Culture negative	36 (17.2)
Polymicrobial	21 (10.0)

ESRD, end-stage renal disease; PD, peritoneal dialysis; RRT, renal replacement therapy; s.d., standard deviation.

Baseline CRP level and short-term adverse outcomes

At baseline, the median CRP value was 56.0 mg/l (25–75th percentile: 22.0–126.0 mg/l). CRP in quartile 1 was $\leqslant$22.0 mg/l, in quartile 2 was 22.1–56.0 mg/l, in quartile 3 was 56.1–126.0 mg/l, and in quartile 4 was $\geqslant$126.1 mg/l.

Short-term adverse outcomes were observed in 72 of 209 (34.0%) patients with a median time to event of 18 days (25–75th percentile: 6–30 days). Thirty-three patients (15.8%) were switched to hemodialysis, at least temporarily; three of these required a laparotomy for bowel wall perforation ($N=2$) or diverticular abscess ($N=1$). Eleven (5.3%) patients died during the course of treatment; three of these had intra-abdominal pathology identified before death (one of each of: bowel wall perforation, gall bladder sepsis, and ischemic bowel). Ten patients (4.8%) demonstrated cytological or culture evidence of persistent infection at week 3, resulting in an extension of antibiotic treatment. Eighteen patients (8.6%) experienced a relapse within 4 weeks of cessation of antibiotic treatment.

Of the 18 patients who relapsed, the initial peritonitis event was caused by Gram-positive organisms other than *Staphylococcus aureus* in eight (44%) patients, polymicrobial infections in four (22%) patients, culture negative infections in three (17%) patients, *Staphylococcus aureus* in two (11%) patients, and a Gram-negative organism in one (6%) patient.

In the univariate logistic regression analysis, the odds ratio (OR) for developing a short-term adverse outcome from peritonitis increased progressively with each quartile of CRP. Compared to the reference group (quartile 1), the OR was 1.90 for quartile 2 (95% CI: 0.75–4.59), 3.01 for quartile 3 (95% CI: 1.24–7.30), and 3.98 (95% CI: 1.66–9.57) for quartile 4. After adjustment for age, gender, diabetes, duration of renal replacement therapy (RRT), and causative organism in the multivariable model, the upper two quartiles of CRP (third quartile: OR 2.73 (95% CI: 1.09–6.87); highest quartile: OR 3.38 (95% CI: 1.36–8.42) compared to quartile 1) and causative organism (OR 2.76 (95% CI 1.48–5.12) for *Staphylococcus aureus*, Gram negatives and polymicrobial infections compared to others) were statistically significantly associated with an increased risk of short-term adverse outcomes. Adjustment for duration of PD in place of duration of RRT did not alter the results. The results of the multivariable model are shown in Table 2.

CRP level at week 3 and long-term adverse outcomes

Three weeks following initiation of antibiotic treatment, 155 of 209 patients met the criteria for resolution of peritonitis. Of these 155 patients, 122 had CRP measurements available

Table 2 | Multivariable model for development of short-term adverse outcomes (switch to hemodialysis, death, persistent infection, and relapse) in PD-associated peritonitis

Variable	OR	95% CI	*P*-value
CRP quartile			
1 (<22 mg/l)	1.0		
2 (24–56 mg/l)	1.57	0.61–4.02	0.35
3 (57–126 mg/l)	2.73	1.09–6.87	0.03
4 (127–288 mg/l)	3.38	1.36–8.42	0.001
Organism			
Non-*S. aureus* Gram-positive cocci and culture negative	1.0		
S. aureus, Gram negative, Polymicrobial	2.76	1.48–5.12	0.001
Male gender	0.87	0.46–1.62	0.65
Diabetes	1.22	0.63–2.37	0.56
Age (per year increase)	1.02	1.00–1.03	0.12
Duration of RRT (per year increase)	1.03	0.97–1.10	0.31

CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; PD, peritoneal dialysis; RRT, renal replacement therapy.

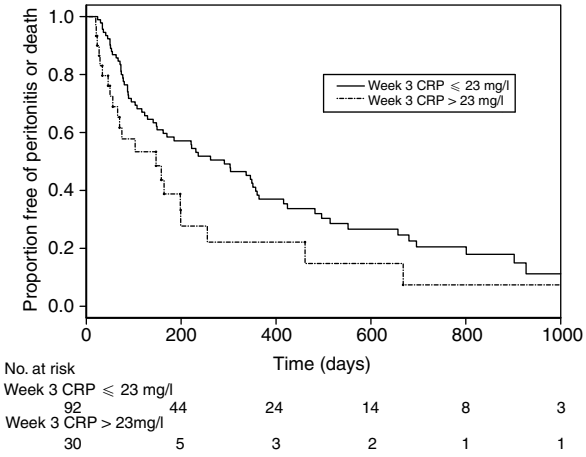

Figure 1 | Time to next peritonitis event or death from any cause. Patients who show resolution of peritonitis at 3 weeks following initiation of antibiotic treatment are stratified by CRP level. Log-rank $P = 0.03$. The number of remaining patients at risk in each group is shown below the figure.

at this time. The median CRP value reported at week 3 was 8.4 mg/l (25–75th percentile: 8.0–23.0 mg/l). Eighty-six of 122 (70.5%) patients experienced a long-term adverse outcome (11 deaths and 75 peritonitis episodes) at a median time of 221 days. The median time to development of long-term adverse outcomes (254 days) and the proportion of patients experiencing an adverse event (69.7%) was similar in the 33 patients with missing values for CRP at week 3.

The Kaplan–Meier survival curves for the development of a subsequent peritonitis event or death from any cause are shown in Figure 1. The time to occurrence of these long-term outcomes was statistically significantly shorter at 147 days in the group with week 3 CRP values in the highest quartile (>23.0 mg/l), compared to 291 days in those with CRP ⩽23.0 mg/l (log rank $P = 0.03$). Of the 30 patients with CRP >23 mg/l at 3 weeks, 17 (57%) had peritonitis caused by Gram-positive organisms other than *Staphylococcus aureus*, ten (33%) were caused by *Staphylococcus aureus*, polymicrobial or Gram-negative organisms, and four (13%) were culture negative.

In the univariate Cox regression analysis, the hazard ratio (HR) for adverse long-term outcomes was 1.71 (95% CI: 1.04–2.82) for patients in the highest quartile of CRP compared to those with lower values. Results of the multivariable Cox model are shown in Table 3. In the adjusted analysis, the HR for long-term adverse outcomes was 1.79 (95% CI: 1.05–3.07) for patients in the highest quartile of CRP compared to the remaining patients. Men were also at statistically increased risk of developing long-term adverse outcomes, with a HR of 1.82 (95% CI: 1.13–2.94) compared to women. Additional adjustment for baseline CRP level did not significantly alter the results of the multivariable model, nor did adjustment for duration of PD in place of duration of RRT.

Table 3 | Multivariable Cox regression model for development of long-term adverse outcomes (subsequent peritonitis event or death from any cause) in patients who demonstrated resolution of peritonitis three weeks after initiation of antibiotic therapy

Variable	HR	95% CI	*P*-value
CRP category			
1 (⩽23 mg/l)	1.0		
2 (>23 mg/l)	1.79	1.05–3.07	0.03
Organism			
Non-*S. aureus* gram-*positive* cocci and Culture negative	1.0		
S. aureus, gram negative, polymicrobial	1.43	0.89–2.29	0.14
Male gender	1.82	1.13–2.94	0.01
Diabetes	1.12	0.70–1.79	0.63
Age>55 years	1.57	0.92–2.69	0.10
Duration of RRT (per year increase)	0.95	0.89–1.01	0.11

CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; RRT, renal replacement therapy.

DISCUSSION

In this prospective cohort study of PD patients presenting with an incident episode of peritonitis, we found that higher baseline levels of serum CRP were associated with an increased risk of short-term adverse outcomes including death, switch to hemodialysis, persistent infection, and relapse of peritonitis. In patients who met clinical and laboratory criteria for resolution of peritonitis 3 weeks after beginning antibiotic treatment, higher CRP levels were associated with an increased risk of long-term adverse events, including a subsequent peritonitis episode or death from any cause. These associations persisted after adjustment for potential confounders, including causative organism. A

predictor of outcome from peritonitis that is easily measured at the time of presentation and routine follow-up is of particular relevance to this group of ambulatory patients who may reside in areas remote from immediate medical attention.

CRP levels are known to increase with declining kidney function.[5] However, the degree of CRP elevation at diagnosis was quite marked in our study, and was many times greater than those reported in 'stable' (noninfected) PD patients, where median levels ranging from 3 to 15 mg/l have been reported.[9,11,12,14] Troidle *et al.*[14] also observed marked elevations of CRP during PD-associated peritonitis. In their study, the mean level of CRP was 118.3 mg/l 48 h after diagnosis. These levels likely reflect the intensity of the inflammatory response and are consistent with the role of CRP in nonspecific immunity as an activator of the complement cascade. As CRP level is associated with an increased risk of short-term adverse outcomes from peritonitis, the degree of CRP elevation is presumably also an indicator of a more severe infection.

By 3 weeks, more than half of our patients had CRP levels in the range reported as 'baseline' levels in other studies of PD patients. As pre-peritonitis CRP levels were not available in all of our patients, we are unable to comment on how many of them had persistent elevations of CRP above their individual baseline levels at this time. Nonetheless, patients with the highest CRP levels at 3 weeks experienced an increased risk of long-term adverse events, which included a combination of a subsequent peritonitis episode or death. The association between elevated levels of CRP and mortality in PD patients has been described in other studies.[9,11] This may be related to the potential role of inflammation in atherogenesis and development of cardiovascular disease.[15] Our sample size was not large enough to demonstrate a statistically significant association between elevated CRP and increased risk of future peritonitis events alone (when censored for death, the HR for development of a subsequent peritonitis event was 1.31 (95% CI 0.61–2.81) for patients in the group with CRP >23 mg/l compared to patients with CRP $\leqslant 23$ mg/l at 3 weeks). Nonetheless, the potential association between elevated CRP and increased risk of future peritonitis events is novel and likely reflects a distinct pathophysiology. For example, persistent elevations of CRP immediately following peritonitis treatment may signal ongoing subclinical infection at the PD catheter exit site or tunnel, which serves as the bacterial source for future infections.

Despite the frequent occurrence of PD-associated peritonitis, it remains difficult to predict which patients will have poor outcomes. Our study is consistent with others that have demonstrated that causative organism (Gram negative, *S. aureus* and polymicrobial infections in particular) is an important predictor of outcome.[2,3,16–18] However, few studies have examined the predictive utility of specific host factors. Krishnan *et al.*[2] studied 399 episodes of peritonitis in 191 individuals and found that the duration of PD and the number of days the PD effluent cell count was >100/ml were independently predictive of nonresolution (death, catheter removal, or transfer to hemodialysis). Duration of dialysis was not predictive of outcomes in our study; we were not able to adjust for the duration of PD effluent cell count $>100/\mu$l as this information was not available in all patients. Also in contrast to our study, Choi *et al.*[19] found that older patients and those with a longer duration of PD were at increased risk for catheter removal in a retrospective study of 64 peritonitis episodes. In one retrospective study of 693 episodes of peritonitis, elevated CRP was associated with greater peritonitis-related mortality; however, only 41 events were available for inclusion in the multivariable model.[3] Our study is unique in its examination of both short- and long-term outcomes following peritonitis, thus expanding the sparse existing literature on this subject.

The strengths of this study are its prospective design, rigorous follow-up, and large size. In addition, the demographic characteristics of our patient population and the distribution of organisms causing peritonitis are typical of those previously reported, supporting the generalizability of our findings to PD patients elsewhere. However, our findings must be interpreted within the limitations of the study design. This was an observational study, and our results may partially reflect residual confounding by unmeasured factors. For example, data was not uniformly available on indicators of disease severity, such as hypotension at diagnosis or admission to an intensive care unit. The CRP assays in this study were not performed at a central laboratory, potentially introducing bias related to interlaboratory variability of measurements. As the CRP elevations observed were quite marked, it is less likely that small differences that may exist between the assays played a large role in biasing our results. In addition, all assays were calibrated according to international standards and adjustment of the multivariable analyses for site of CRP measurement did not significantly alter our results. Finally, the CRP assays used were not the highly sensitive type. However, the degree of CRP elevation associated with adverse outcomes following PD-associated peritonitis did not require a highly sensitive assay for detection. Furthermore, the assays used would be expected to produce similar results to a highly sensitive assay within the range of values observed in our study.

We used duration of RRT as a proxy for residual renal function in our analyses. Similar methods were used by Krishnan *et al.*,[2] where duration of PD was entered into the multivariable model. When we investigated the effect of residual renal function in patients with available data ($N=143$), it was not associated with either short- or long-term adverse outcomes in univariate analyses. One possible explanation for this lack of statistical association is that residual renal function measurements were taken at variable time intervals before the onset of peritonitis (as the timing of infection was unpredictable) and, as a result, may not have reflected the true residual renal function at the time of infection.

In conclusion, in patients presenting with an episode of PD-associated peritonitis, a higher level of CRP is independently associated with an increased risk of short- and long-term adverse outcomes. This result identifies a potential role for serial measurement of this inflammatory marker during the course of antibiotic treatment to identify patients at greater risk of treatment failure. Our study suggests that those with a CRP level >57 mg/l at diagnosis may be at particular risk. However, whether patients with the most marked elevations of CRP would benefit from a more aggressive strategy of investigation, monitoring, and treatment of PD-associated peritonitis requires further study.

MATERIALS AND METHODS

Subjects

This was a prospective cohort study of 209 patients on continuous PD followed at the Oxford Kidney Unit (United Kingdom) and its satellite facilities (Milton Keynes and High Wycombe Renal Units) who presented with an incident episode of PD-associated peritonitis between 1 January 1999 and 31 March 2005. The incident episode of peritonitis was defined as the first episode of peritonitis experienced by the patient since the initiation of PD. All patients had double cuff silastic PD catheters placed using sterile surgical technique.

Demographic and clinical characteristics were determined at the time of PD initiation. End-stage renal disease was classified as follows: diabetes mellitus (type 1 or 2), glomerulonephritis, or other causes. Patients were recorded as having cardiovascular disease if they had a history of cerebrovascular disease, ischemic heart disease, congestive heart failure, or peripheral vascular disease.

Diagnosis of peritonitis

Criteria for the diagnosis of peritonitis were: cloudy dialysate and an elevated dialysate WCC of more than 100/mm^3, in accordance with published guidelines from the International Society of Peritoneal Dialysis.[20] In cases where fluid WCC was unavailable, cloudy fluid and/or abdominal pain accompanied by a positive fluid culture was considered diagnostic ($N=5$).

Treatment and follow-up

All patients were assessed by PD unit/renal ward nurses and reviewed by a physician at diagnosis. Empiric treatment consisted of intraperitoneal vancomycin (single dose of 1.5 g in patients <60 kg; 2 g in patients >60 kg) and oral ciprofloxacin (initial dose 1 g, followed by 500 mg twice daily). Antibiotic treatment was subsequently tailored once antimicrobial sensitivities were available. The standard duration of antibiotic treatment was 2 weeks. Treatment for longer than 2 weeks was left to the discretion of the physician. Routine follow-up visits were scheduled at 1 and 3 weeks following initiation of treatment. PD catheters were removed and patients were switched to hemodialysis if they demonstrated a lack of improvement within the first week of appropriate antibiotic therapy, if peritoneal dialysate specimens grew yeast species at any time during follow-up, if a clinically apparent tunnel infection was present at diagnosis, and/or if a laparotomy was required for intra-abdominal pathology (e.g. bowel perforation).

Laboratory measurements

PD fluid was sent for Gram stain, cell count, culture and sensitivity at the time of presentation, and then at 1 and 3 weeks following initiation of antibiotic treatment. Blood samples were sent for CRP levels at baseline (within 48 h of diagnosis) and 3 weeks (range: 17–25 days) following initiation of antibiotic treatment. CRP levels were determined by immunoturbidimetry at three institutions. In Oxford, reagents were supplied by Abbott Laboratories (Abbott Park, IL, USA) and the lower reporting limit was 8 mg/l; in Milton Keyes and High Wycombe, reagents were supplied by Beckman Coulter Inc. (Fullerton, CA, USA) and the lower reporting limit was 5 mg/l. Assays were calibrated according to National and International Federation of Clinical Chemistry (IFCC) guidelines. The coefficients of variation were $<5\%$ for both assays. Other laboratory investigations, such as complete blood counts and serum chemistry, were performed at the discretion of the treating physician.

Definitions of outcome variables

Peritonitis was defined as resolved if the PD fluid WCC was <100/mm^3, PD fluid cultures were negative and/or patients experienced a clinical resolution at completion of the intended course of antibiotic treatment.

Short-term adverse outcomes included death during the course of peritonitis treatment, switch to hemodialysis during the course of peritonitis treatment, persistent infection (failure to achieve cytological and/or culture remission after the intended duration of antibiotic treatment), and relapse (any PD fluid with WCC >100 mm^3 within 4 weeks of cessation of antibiotic therapy, regardless of whether or not PD fluid culture results were positive). Patients with resolved peritonitis at 3 weeks were followed for the development of the following long-term outcomes of interest: peritonitis occurring any time after cessation of antibiotic therapy and death from any cause.

Statistical analysis

Baseline characteristics were summarized as mean (± 1 s.d.), median (25–75th percentile), or proportions (percent), as appropriate.

Baseline CRP and short-term outcomes. Baseline CRP measurements were divided into quartiles, from the lowest to the highest levels. Logistic regression analysis was used to determine the association between baseline CRP and short-term adverse outcomes. A multivariable logistic regression model was used to adjust for the following potential confounders, determined *a priori*: age, gender, diabetes, duration of RRT, and causative organism (Group 1: Culture negative infections and non-*Staphylococcus aureus* Gram-positive infections; Group 2: *Staphylococcus aureus*, Gram negative and polymicrobial infections). Complete data was available on all of these covariates.

Week 3 CRP and long-term outcomes. Week 3 CRP levels were initially divided into quartiles and the association between CRP level and development of the long-term adverse outcomes of interest (death from any cause, subsequent peritonitis event) was explored using the Kaplan–Meier method. Because patients in the lower three quartiles of CRP had a similar time to event, they were grouped together and compared to those in the highest quartile of CRP using the log-rank test. Cox regression analysis was used to determine the HR for long-term adverse outcomes, comparing the highest quartile of CRP levels to the remaining patients, adjusting for age, gender, diabetes, duration of RRT, and causative organism. Patients were censored at the time of transplantation, switch to hemodialysis for reasons other than peritonitis, transfer of care out of the region, and end of follow-up. The proportional hazards assumption was tested using log-negative-log plots and time-dependent covariates in the

Cox model. When age was entered into the model as a continuous variable, the proportional hazards assumption was violated, thus, a binary variable was created for age ($\leqslant 55$ versus >55 years old), which met the proportional hazards assumption.

All P-values are two-tailed and P-values <0.05 were considered to be statistically significant. All analyses were performed with SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

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