Predictive Value of Dialysate Cell Counts in Peritonitis Complicating Peritoneal Dialysis

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Early prediction of outcomes has major potential implications regarding the management of dialysis-related peritonitis. The outcomes of 565 consecutive episodes of peritonitis complicating peritoneal dialysis between August 2001 and July 2005 were evaluated in relation to the dialysate cell counts. Discriminatory power, based on the area under the receiver-operating characteristic (ROC) curves, of the cell counts was assessed. The findings then were validated externally in a cohort of 217 peritonitis episodes from another dialysis unit. During the study period, 565 episodes of peritonitis were included for analysis, 465 of which had treatment success defined as complete resolution of peritonitis without the need for Tenckhoff catheter removal. Of the remaining 100 episodes (treatment failure), 70 required Tenckhoff catheter removal and 30 had peritonitis-related death. The peritoneal dialysate total white blood cell count on day 3 of peritonitis predicted treatment failure independent of standard risk factors, and it had a higher area under the ROC curve than the dialysate white cell count on day 1 (0.80 versus 0.58; P < 0.0001). Using a peritoneal dialysate white count cut point ≥1090/mm³ on day 3, the sensitivity was 75% and the specificity was 74% for the prediction of treatment failure (defined as catheter loss or peritonitis-related death). In multiple logistic regression analyses, peritoneal dialysate white count ≥1090/mm³ on day 3 was an independent prognostic marker for treatment failure after adjustment for conventional risk factors (hazard ratio 9.03; 95% confidence interval 4.40 to 18.6; P < 0.0001). Number of years on peritoneal dialysis; diabetes; Gram-negative organisms; and Pseudomonas, fungal, or Mycobacterium species were other independent risk factors that were predictive of treatment failure. Findings from an independent validation set of peritonitis (217 episodes after exclusion of Mycobacterium and fungal causes) also favored the peritoneal dialysate white count on day 3, as compared with day 1 and day 2, to predict treatment failure. Area under the ROC curve for the white counts on day 3 was 0.98 (95% confidence interval 0.95 to 0.99) in the validation set. This study demonstrated and cross-validated the superiority of peritoneal dialysate white cell count on day 3 to predict outcomes of dialysis-related peritonitis. These results call attention to the value of validating prognostic factors of peritonitis complicating peritoneal dialysis.


Peritonitis is a serious infectious complication that accounts for significant morbidity and the majority of catheter loss in patients who undergo peritoneal dialysis (1,2). Challenges to improving the quality of care for dialysis-related peritonitis occur at multiple levels. The first step to improving the treatment outcome is to stratify individual peritonitis episodes to allow prompt adjustment and modification of the antibiotic regimen. Currently, patients receive initial empiric therapy before knowledge of the causative organism according to the International Society for Peritoneal Dialysis (ISPD) and contemporary treatment guidelines (3–5). We believe that better choice of antimicrobial therapy or treatment strategy can be made if severity of peritonitis can be established on the basis of early findings. Specifically, our hypothesis was that early peritoneal dialysate white blood cell counts allow prediction of the severity of a dialysis-related peritonitis.

To determine whether dialysate white blood cell counts, among other clinical parameters, can predict peritonitis outcomes, we conducted a retrospective study to evaluate prognostic factors of dialysis-related peritonitis outcomes. The prognostic performance of peritoneal dialysate white cell count was confirmed further in another independent validation data set.

Materials and Methods

The first part of our study took place between August 2001 and July 2005 in a single dialysis unit at the Prince of Wales Hospital. All consecutive peritoneal dialysis patients who presented with peritonitis in our center were recruited. The diagnosis of peritonitis complicating peritoneal dialysis was based on at least two of the following criteria: Abdominal pain or cloudy peritoneal dialysis effluent, leucocytosis in peritoneal fluid effluent (white blood cell count at least 100/mm³), or positive Gram stain or culture from effluent (3). Bacterial culture of
peritoneal dialysis effluent in our unit was performed using the Bac-TAlert bottles (Organon Teknika Corp., Durham, NC) following the manufacturer's instructions. Patients were instructed to bring the first cloudy fluid or come to the dialysis center immediately. For each episode of peritonitis, we recorded the initial peritoneal dialysate white blood cell count and then the serial white blood cell counts on scheduled follow-up visits (days 3 and 5). Cell counts were obtained by placing an aliquot (3 to 5 ml) of drained fluid immediately into EDTA tubes. Peritonitis episodes were treated with the standard antibiotic protocol of our center, in accordance with the latest ISPD guidelines (4). Initial antimicrobial therapy for peritonitis consisted of intraperitoneal administration of cefazolin and cefazidime. Intravenous antibiotics were used when the patient seemed septic clinically. Prophylactic oral nystatin 500,000 U three times daily was used with concomitant antibiotics in all cases. The antibiotics were modified once the culture results and sensitivities became available. In general, patients received antibiotics for 14 d (3,4). When *Pseudomonas or Xanthomonas* species were isolated, patients received two antibiotics, which were continued for at least 21 d (3,4,6). When *Staphylococcus aureus* was isolated, patients were treated for at least 21 d. Relapse of peritonitis was defined as recurrence of peritonitis by the same organism within 30 d of completion of the antibiotic treatment (4,7). In general, Tenckhoff catheters were removed when the dialysis fluid did not clear by day 10 (6). Alternatively, if the peritonitis fails to respond to appropriate antibiotics within 5 d, the catheter will be removed as suggested by the ISPD guidelines (4). The exact time of catheter removal varied among patients depending on the availability of operating theater.

For each episode of peritonitis, we also recorded the patient age at the time of peritonitis, gender, presence of diabetes, duration of peritoneal dialysis before the onset of the peritonitis episode, and the causative microorganisms. Clinical information was abstracted from the medical files and central renal replacement therapy registry.

Our primary goal was prediction of treatment outcome (dichotomized as success and failure) in peritoneal dialysis–related peritonitis. Treatment success was defined as complete resolution of peritonitis using antibiotics alone, without the need for Tenckhoff catheter removal. Conversely, treatment failure referred to the patients who either died of the peritonitis episodes or required Tenckhoff catheter removal. Death related to peritonitis was defined as death of a patient with active peritonitis or admission of a patient with peritonitis or within 2 wk of a peritonitis episode (4). Relapse of peritonitis, by itself, was not considered treatment failure.

For the validation study, we studied consecutive patients with peritonitis from another dialysis unit (at United Christian Hospital) between January 2004 and December 2005. We excluded patients who had *Mycobacterium* and fungal peritonitis because they have a high treatment failure rate, and, in the derivation cohort, such infection is an indication for catheter removal. Treatment protocol and case definition were otherwise similar to our primary cohort except the antimicrobial policy; cefazolin and gentamicin were used as empirical regimens during the study period.

### Statistical Analyses

Statistical analysis was performed by SPSS for Windows software version 13.0 (SPSS Inc., Chicago, IL) and SAS system software version 8.2 (SAS Institute, Cary, NC). All data were expressed as mean ± SD for normally distributed data and median or range for skewed data. Data that were not normally distributed, such as the total white cell counts in the dialysate (which display a positively skewed distribution), were transformed logarithmically before analysis. To evaluate the discriminating ability of dialysate white blood cell counts, we performed receiver operating characteristic (ROC) analysis for log-transformed cell count on day 3 in comparison with day 1. To identify the cutoff levels that maximized the sensitivity and specificity, we calculated the area under the ROC curve (AUC); sensitivity and specificity at each threshold white cell count cutoffs were determined (8). We used multiple logistic regression to examine predictors for treatment failure. Our model-building strategy was constructed as follows. In the multivariate model, explanatory variables that encompassed covariates that were identified by our investigation and previous studies (9,10) were examined. Odds ratios and 95% confidence intervals (CI) were calculated. All probabilities were two-tailed, and the level of significance was set at 0.05.

### Results

A total of 565 episodes of peritonitis in 280 peritoneal dialysis patients were recorded between August 2001 and July 2005. The median time of peritonitis episodes since the beginning of peritoneal dialysis was 36 mo. Of the 565 episodes in the analytic sample, the majority (44%) were due to Gram-positive organisms only. There were 76 (14%) episodes of culture-negative peritonitis and 43 (8%) relapse episodes. Treatment success, defined as complete resolution of peritonitis using antibiotics alone without the need for Tenckhoff catheter removal, occurred in 465 (82%) episodes. Of the remaining 100 (18%) episodes with treatment failure, approximately one third (30 episodes) resulted in mortality (a fatality rate of 5%), and 70 episodes required Tenckhoff catheter removal. Peritoneal dialysate total white count varied from 10 to 80,600/mm³ (median 460; interquartile range 90 to 1508/mm³) on day 3.

Demographic and clinical characteristics are presented in Table 1, categorized by whether the peritonitis episodes had treatment success or failure. Among the demographic variables, age (relative risk [RR] 0.99; 95% CI 0.98 to 1.02), and gender (RR 1.36; 95% CI 0.88 to 2.11) were not significantly associated with the odds of treatment failure on bivariate analysis. Of note, patients with treatment failure of peritonitis episode were more likely to have diabetes (RR 3.44; 95% CI 1.68 to 7.04) and had undergone a longer period of dialysis (hazard ratio [HR]; each year increase in duration of dialysis] 1.12; 95% CI 1.05 to 1.20; *P* = 0.001). The peritoneal dialysate white count on day 3 was significantly (*P* < 0.0001) higher in the treatment failure group then in the treatment success group (median 3090/mm³ [range 10 to 80,600] versus 340/mm³ [range 10 to 43,700]).

The ROC curves (Figure 1) depicted the true-positive fractions (sensitivity) and false-positive fractions (1 – specificity) at various cut points for dialysate white blood cell counts. The calculated AUC for the natural log-transformed white counts on days 1 and 3 was 0.58 (95% CI 0.51 to 0.64) and 0.80 (95% CI 0.75 to 0.85), respectively. Sensitivity and specificity analyses confirmed that the ROC curve of log-transformed dialysate white counts on days 1 and 3 both were significantly different from no discrimination (*P* = 0.02 and *P* < 0.0001, respectively) in predicting treatment failure. However, the performance of cell count on day 3 was superior to that of on day 1; pair-wise comparison of AUC showed that dialysate white count on day 3 had a better discriminating ability than that on day 1 (*P* < 0.0001). On the basis of examination of the ROC curve, the dialysate white count on day 3 that optimized sensitivity and
specificity was approximately 1090/mm$^3$. For a peritoneal dialysate white count $\geq 1090$/mm$^3$ on day 3, the sensitivity was 75% and the specificity was 74% for the prediction of treatment failure. In this setting, the cut point $\geq 1090$/mm$^3$ had an accuracy of 75%, 35% positive predictive value, and 94% negative predictive value to predict treatment failure. When we excluded episodes of fungal peritonitis, because they have a high treatment failure rate in general, the AUC of log-transformed peritoneal dialysate white cell count on day 3 remained similar (0.84; 95% CI 0.79 to 0.90).

With respect to individual treatment outcomes, dialysate cell count on day 3 also demonstrated better prognostic value than that on day 1 to predict either Tenckhoff catheter removal or mortality attributable to peritonitis. The AUC that was generated to test the predictive accuracy for Tenckhoff catheter removal by the log-transformed white counts on 3 was 0.79 (95% CI 0.73 to 0.84), whereas the corresponding AUC for predicting peritonitis-related death was 0.77 (95% CI 0.68 to 0.86).

Multiple logistic regression was performed to examine predictors for treatment failure with a model that was constructed from variables that encompassed covariates that were identified by our investigation and previous studies (9,10). As shown in Table 2, number of years on dialysis therapy; diabetes; Gram-negative organisms; and Pseudomonas, fungal, or Mycobacterium species were found to be independent risk factors for treatment failure. In this model, a peritoneal dialysate white count $\geq 1090$/mm$^3$ on day 3 was found to be an independent predictor of treatment failure (odds ratio [OR] 9.03; 95% CI 4.40 to 18.6; $P < 0.0001$). Exclusion of fungal peritonitis episodes did not materially influence the results (data not shown); peritoneal dialysate white count $\geq 1090$/mm$^3$ on day 3 remained a strong predictor of treatment failure (OR 10.2; 95% CI 4.85 to 21.4; $P < 0.0001$). In another regression model that tested for possible predictive factor of peritoneal dialysate white cell count $\geq 5$/mm$^3$ (10) (Table 3), it showed a significant association with treatment failure (OR 7.38; 95% CI 3.38 to 16.1; $P < 0.0001$).

To assess the prognostic performance of peritoneal dialysate white cell count, we further focused our analyses in another independent validation data set with different case mix and practice settings. Within this cohort of 217 consecutive peritonitis episodes from the second dialysis unit, the culture-negative rate and treatment failure rate were 12 and 7%, respectively. Validation set characteristics are summarized in Table 4.
For evaluation of the significance of peritoneal dialysate cell count on day 3 as predictor for treatment outcome, the ROC curves (Figure 2) were performed at various cut points for dialysate white blood cell counts. The calculated AUC for the natural log-transformed white counts on day 3 (0.98; 95% CI 0.95 to 0.99) was significantly larger than for day 1 (0.69; 95% CI 0.57 to 0.81) and day 2 (0.71; 95% CI 0.58 to 0.85; both \( P < 0.0001 \)). For practical purposes, the previously suggested cut point of \( \geq 1090/\text{mm}^3 \) at day 3 is rounded to \( \geq 1000/\text{mm}^3 \) to maximize the clinical usefulness without materially altering the accuracy of a prognostic factor. When the peritoneal dialysate white count cut point \( \geq 1000/\text{mm}^3 \) at day 3 was applied to the validation set, it had a sensitivity of 64% and a specificity of 97% for the prediction of treatment failure. This chosen cutoff demonstrated a satisfactory positive predictive value to predict treatment failure when applied to our cross-validation group; if the peritoneal dialysate white count is \( \geq 1000/\text{mm}^3 \) at day 3, then the treatment will fail 64% of the time.

**Discussion**

The results of this study demonstrate that several demographic characteristics (diabetes and duration of peritoneal di-
analysis before peritonitis episodes) and early clinical findings (peritoneal dialysate total white count on day 3) of patients who are on peritoneal dialysis are predictive of the response to treatment. One of the important and novel findings was the significant association between peritoneal dialysate white cell count on day 3 and the peritonitis outcome. To minimize the play of chance or overfitting phenomenon, we first evaluated the performance or prognostic value of dialysate white cell count on day 3 in a series of 565 peritonitis episodes and then validated it in another, new set of peritoneal dialysis patients with 217 peritonitis episodes. On the basis of our initial study cohort of 565 peritonitis episodes, we found that a cutoff peritoneal dialysate white count of $10^9$ /mm$^3$ on day 3, independent of conventional host and bacterial risk factors such as the presence of diabetes or fungal or Pseudomonas organisms, carried a ninefold increased risk for treatment failure. To be of practical clinical value, the peritoneal dialysate total white cell count is readily available with relatively low cost and rapidly enough to influence clinical decision making and, most important, to add independent information about the risk for adverse outcome. The validity of this prognostic parameter is bolstered by the concordance between the results from the primary study cohort and the validation set.

Our findings will be useful at several key stages in the management of dialysis-related peritonitis. First, in light of the prognostic information, cell count measurement probably should be repeated on day 3 of peritonitis on a routine basis. Second, on the basis of these predictive factors, the severity of peritonitis could be established early.

Few studies have evaluated the ability of peritoneal dialysate cell counts and other factors to predict treatment outcomes (11). Shah et al. (9) evaluated 57 episodes of bacterial peritonitis in 25 continuous ambulatory peritoneal dialysis patients and demonstrated that peritoneal white cell and polymorphonuclear counts on day 3 but not day 2 had predictive value of peritonitis episodes that require removal of Tenckhoff catheters. This was a select sample with peritonitis episodes treated before the 1996 revision of the ISPD guidelines. The finding, nevertheless, concurs with us that peritoneal dialysate cell count on day 3 performed better in outcome prediction. Because treatment responses are weighed heavily by the microbiological factor

### Table 4. Peritonitis characteristics in the validation set, categorized according to the outcomes of treatment success versus failure

<table>
<thead>
<tr>
<th>Treatment Success</th>
<th>Treatment Failure</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of peritonitis episodes</td>
<td>191</td>
<td>16</td>
</tr>
<tr>
<td>Age (yr; mean ± SD [range])</td>
<td>62 ± 12 (22 to 82)</td>
<td>64 ± 8 (45 to 74)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>102/89 (53%/47%)</td>
<td>9/7 (56%/44%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>100 (52%)</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>Duration of peritoneal dialysis (mo; mean ± SD [range])</td>
<td>38 ± 31 (0.5 to 147)</td>
<td>38 ± 33 (0.5 to 105)</td>
</tr>
<tr>
<td>Peritoneal dialysis modality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intermittent peritoneal dialysis (break-in period)</td>
<td>3 (2%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>continuous ambulatory peritoneal dialysis</td>
<td>182 (95%)</td>
<td>15 (94%)</td>
</tr>
<tr>
<td>automated peritoneal dialysis</td>
<td>6 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Causative organisms</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gram-positive only</td>
<td>91 (48%)</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>Gram-negative only$^b$</td>
<td>49 (26%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pseudomonas or Xanthomonas</td>
<td>13 (7%)</td>
<td>7 (43%)</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>13 (7%)</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Culture negative</td>
<td>25 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Relapse peritonitis episode</td>
<td>16 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Peritoneal dialysate white count $\geq 10^9$/mm$^3$ on day 3</td>
<td>5 (3%)</td>
<td>9 (64%)</td>
</tr>
</tbody>
</table>

$^a$Treatment failure is defined as catheter loss or peritonitis-related death.

$^b$Excluding Pseudomonas and Xanthomonas species.
and *in vivo* response to antibiotics, it might take approximately 3 d for the antibiotic to alter the course of infection. The superiority of peritoneal dialysate cell count on day 3 is not surprising because it simply incorporates the factor of the antibiotics’ effect.

In a subsequent retrospective study of 399 peritonitis episodes, Krishnan et al. (10) reported that when the peritoneal dialysate cell counts exceeded 100/mm³ for >5 d, the odds of treatment failure were significantly higher, similar to our findings in the multiple logistic regression analysis. However, most causative organisms would have been identified by day 5 and the need to gauge the peritonitis severity would become less essential. After all, it is recommended by the current ISPD guidelines that patients who have unresolved cloudy effluent while on appropriate antibiotics after 5 d are to have their Tenckhoff catheters removed (4). To be of clinical relevance, dialysate white cell counts during the early course of illness (within 3 d of peritonitis as compared with day 5) would be more valuable to the clinicians who might desire to refine promptly the treatment strategy and antimicrobial therapy on the basis of the severity of peritonitis.

The mediocre performance of baseline white cell count on day 1 (with AUC of 0.58 as compared with 0.80 for cell count on day 3) can be anticipated, because the timing of initial dialysate effluent collection might not be standardized enough. The day 1 white cell counts were derived from samples that were collected at the time of presentation to the dialysis unit, whereas the number of cells in the peritoneal effluent depends in part on the length of the dwell (4,12). Such inherent propensity to random measurement error for white cell count on day 1 therefore can lead to “noise” that gets in the way of our derivation of prognostic information.

Our study has several limitations. First, the peritoneal dialysate total white cell counts, as opposed to polymorphonuclear leukocyte counts, were measured. Another limitation of our study is that, in contrast to previous studies (10,13,14), we did not examine the effect of a concomitant purulent exit site on the peritonitis response. Finally, although we provide compelling evidence that this parameter performed well for prognosis, we left unanswered whether anything can be done to “treat” the figures. It is especially pertinent to confirm whether aggressive intervention in response to the peritoneal dialysate white cell count on day 3 can translate into clinical benefit.

**Conclusion**

We have demonstrated the ability of peritoneal dialysate white cell count on day 3 to predict peritonitis outcomes. Besides its excellent predictive power with regard to outcome, the peritoneal dialysate total white cell count is easy to obtain. This makes it a practical tool of potentially widespread applicability. Should it be validated prospectively in another cohort of peritoneal dialysis patients with interventional measures, this noninvasive and promising parameter may offer opportunities for early establishment of the severity of peritonitis and potentially more rational choice of antimicrobial therapy or treatment strategy.

**Acknowledgments**

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**References**
