THE ROLE OF NGAL IN PERITONEAL DIALYSIS EFFLUENT IN EARLY DIAGNOSIS OF PERITONITIS: CASE-CONTROL STUDY IN PERITONEAL DIALYSIS PATIENTS

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◆ **Background:** Peritoneal dialysis (PD) is frequently complicated by high rates of peritonitis, which result in hospitalization, technique failure, transfer to hemodialysis, and increased mortality. Early diagnosis, and identification of contributing factors are essential components to increasing effectiveness of care. In previous reports, neutrophil gelatinase-associated lipocalin (NGAL), a lipocalin which is a key player in innate immunity and rapidly detectable in peritoneal dialysis effluent (PDE), has been demonstrated to be a useful tool in the early diagnosis of peritonitis. This study investigates predictive value of PDE NGAL concentration as a prognostic indicator for PD-related peritonitis.

◆ **Methods:** A case-control study with 182 PD patients was conducted. Plasma and PDE were analyzed for the following biomarkers: C-reactive protein (CRP), blood procalcitonin (PCT), leucocytes and NGAL in PDE. The cases consisted of patients with suspected peritonitis, while controls were the patients who came to our ambulatory clinic for routine visits without any sign of peritonitis. The episodes of peritonitis were defined in agreement with International Society for Peritoneal Dialysis guidelines. Continuous variables were presented as the median values and interquartile range (IQR). Mann-Whitney U test was used to compare continuous variables. Univariate and multivariate logistic regression were used to evaluate the association of biomarkers with peritonitis. Receiver operating characteristic (ROC) curve analysis was used to calculate area under curve (AUC) for biomarkers. Finally we evaluated sensitivity, and specificity for each biomarker. All statistical analyses were performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

◆ **Results:** During the 19-month study, of the 182 patients, 80 had a clinical diagnosis of peritonitis. C-reactive protein levels ($p < 0.001$), PCT ($p < 0.001$), NGAL in PDE ($p < 0.001$), and white blood cells (WBC) in PDE ($p < 0.001$) were all

significantly different in patients with and without peritonitis. In univariate analysis, CRP (odds ratio [OR] 1,339; $p = 0.001$), PCT (OR 2,473; $p < 0.001$), WBC in PDE (OR 3,986; $p < 0.001$), and NGAL in PDE (OR 36.75 $p < 0.001$) were significantly associated with episodes of peritonitis. In multivariate regression analysis, only WBC (OR 24.84; $p = 0.012$), and peritoneal NGAL levels (OR 136.6; $p = 0.01$) were independent predictors of peritonitis events. Moreover, AUC for NGAL in peritoneal effluent was 0.936 ($p < 0.001$) while AUC for CRP, PCT, and WBC count in peritoneal effluent were 0.704 ($p = 0.001$), 0.762 ($p = 0.039$), 0.975 ($p < 0.001$), respectively. Finally, combined WBC and peritoneal NGAL test increased the specificity (= 96%) of the single test.

◆ **Conclusions:** These results identify NGAL in peritoneal effluent as a reliable marker of peritonitis episodes in PD patients. Collectively, our findings demonstrate that the use of peritoneal NGAL cooperatively with current clinical diagnostic tools as a prognostic indicator, presents a valuable diagnostic tool in PD-associated peritonitis.

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Peritonitis is a frequent complication in peritoneal dialysis (PD) patients. While widespread improvements have been made, the incidence of PD-associated peritonitis is still a major cause of morbidity and mortality (1). The current clinical criteria for the diagnosis of peritonitis includes clinical signs and symptoms, cloudy effluent, and positive culture (2). However, in the first hours of clinical presentation, such criteria may be inadequate in some conditions and delay early treatment. Clinical signs and symptoms are not always discriminative in the early recognition of peritonitis: abdominal pain, nausea/vomiting, diarrhea or constipation are often absent in a wide segment of PD patients with peritonitis

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(2). On the other hand, white blood cell (WBC) count in peritoneal dialysis effluent (PDE), a key diagnostic marker, is not devoid of false negative and false positive results (3). Slight changes in storage conditions of PDE by hospital staff, different local peritoneal conditions, and laboratory analysis process can affect the accuracy of WBC counts. Finally, the culture of peritoneal effluent is not available in the first hour of peritonitis, further complicated by reliability of Gram evaluation in the diagnosis of peritonitis in PD patients (4). For all these reasons, a myriad of biomarkers have been evaluated in this clinical setting, including adipokine (5), matrix metalloproteinase-9 (6), nitric oxide (7), tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6), and interleukin-8 (IL-8) (8). Regrettably, none of these biomarkers seems to have broad spread applicability in the clinical setting. In this scenario, where the decision to start treatment is mainly guided by WBC count, another diagnostic marker could be useful to assist the physician to take the correct treatment action.

Glycoproteins commonly used as blood-based biomarkers play a major role in the body's defense as components of the cell membrane and as antigenic determinants. Lipocalins are a family of glycoproteins that have emerged with considerable interest both because of their small size, relative stability, and critical role in pathologic states. A key target of clinical interest in this family is neutrophil gelatinase-associated lipocalin (NGAL), a small 25-kDa lipocalin normally expressed in low levels *in vivo* by cardiomyocytes, lymphocytes, and renal tubular cells, and increased by orders of magnitude in response to injurious stimuli (9). Neutrophil gelatinase-associated lipocalin, otherwise known as siderocalin, lipocalin-2, uterocalin, and 24p3 is induced in bacterial infection, attenuating pericellular as well as cellular labile iron by sequestering bacterial iron chelators (10). Neutrophil gelatinase-associated lipocalin is readily assayed in a wide variety of pathologies including diagnosis of infection (11–13). Previous studies have reported significant increases of NGAL during peritonitis. Specifically, Axelsson *et al.* demonstrated severe acute peritonitis was accompanied by an increase of NGAL levels in plasma and in peritoneal exudates (14). Similarly, 2 studies reported an increase of NGAL levels in PDE during peritonitis (15,16). Finally, in a preliminary study, we reported NGAL levels in peritoneal effluent (peritoneal NGAL) as a putative indicator for the early diagnosis of peritonitis (17). However, the available studies in PD patients have been limited by study size. The aim of the present study is to validate the utility of peritoneal NGAL for the diagnosis of peritonitis in an adequate size cohort of peritoneal dialysis patients.

METHODS

A case-control study was carried out at the Peritoneal Dialysis Center at San Bortolo Hospital in Vicenza, Italy from January 2011 to July 2012. This study has been designed in accordance with the Helsinki Accords and approved by the local Ethics Committee. End-stage renal disease patients who had been treated with PD for a minimum of 90 days and met inclusion criteria were enrolled. Specifically, inclusion criteria were: age over 18 years, PD treatment for at least 90 days, and informed consent; while exclusion criteria were: the presence of a peritonitis episode 30 days before enrollment.

The case group was composed of eligible patients who arrived at our center with signs and symptoms suggestive of peritonitis, while the control group was composed of patients (without any sign or symptom of peritonitis) who were scheduled in the PD timetable for routine visits immediately after a patient with suspected peritonitis. Specifically, when more than 1 patient with suspected peritonitis came to our center at the same time, we enrolled the controls according to the order of the PD timetable.

All patients underwent blood and peritoneal dialysate effluent analysis at the time of enrollment, to evaluate the level of serum procalcitonin (PCT) and C-reactive protein (CRP), WBC count in PDE, peritoneal NGAL, and microbiological examination. At the same time, we evaluated the following clinical features: age, etiology of chronic kidney disease, comorbidity, dialysis type, clinical aspects of PD therapy such as the type of transporter and the adequacy dialysis indexes.

Peritonitis was defined at the end of the peritonitis episode according to the criteria of the International Society for Peritoneal Dialysis guidelines (2). Specifically, the diagnosis of peritonitis was made when 2 of the following features were present:

1. Clinical signs and symptoms of peritoneal inflammation: pain, discomfort, nausea/vomiting, diarrhea, or constipation.
2. Cloudy drainage with WBC > 100 cells/mm³ (with at least 50% polymorphonuclear cells)
3. Positive culture or Gram stain.

LABORATORY MEASUREMENTS

Microbiological examination, NGAL, and WBC count in peritoneal effluent were evaluated by overnight collection of PDE in the control group, while PDE analysis was evaluated in any suspicious drainage in the case group. For NGAL analysis, all PDE samples were aliquoted and stored at -80°C prior to assay, and were subsequently

measured by Architect platform (Abbott Diagnostics, Abbott Park, IL, USA), using chemiluminescent micro-particle immunoassay technology.

STATISTICAL ANALYSIS

The cohort sample size was evaluated using the Fleiss formula with continuous correction with 2-sided significance level (1-alpha) of 95%, power (1-Beta) of 80%, including ratio of sample size of 1:1; using the odds ratio (OR) of our preliminary results (17). The sample size resulted in 63 patients each for both the case group and the control group. Moreover, in order to obtain a significant logistic multivariate regression, we enrolled patients consecutively into peritonitis case group and control group until 20 peritonitis cases for each variable could be involved in multivariable analysis (CRP, PCT, WBC count, and peritoneal NGAL), for a planned number of peritonitis equal to 80. According to this evaluation, we planned to stop the enrollment when we obtained a clear diagnosis of peritonitis in 80 patients.

The predictive efficacy of all biomarkers for peritonitis diagnosis was evaluated using receiver operating characteristic (ROC) curve analysis, with the area under the ROC curve (AUC).

Moreover, we measured the performance of biomarkers, according to classification function, by sensitivity (number of patients with peritonitis and with positive test/number of patients with peritonitis $\times 100$), specificity (number of patients without peritonitis and with negative test/number of patients without peritonitis $\times 100$), false negative (number of patients with peritonitis and with negative test/number of patients with peritonitis $\times 100$) and false positive value (number of patients without peritonitis and with positive test/number of patients without peritonitis $\times 100$). We considered the test positive if the value was over the reference interval of our laboratory, specifically CRP > 0.5 mg/dL, PCT > 0.5 ng/mL, and WBC in PDE $> 0.1 \times 10^9/L$; while the reference interval for peritoneal NGAL was estimated by ROC curve analysis as the best cutoff value capable of identifying peritonitis episode. Finally, we tested PDE biomarkers in combination to evaluate possible benefits in the diagnosis of peritonitis. Specifically, we considered the 2 possible arrangements: WBC and peritoneal NGAL where both tests resulted positive, and WBC or peritoneal NGAL where only 1 test was positive.

All continuous variables were reported as median values and interquartile range (IQR), while categorical variables were described as percentages. All biomarkers were evaluated by Shapiro-Wilk test to evaluate the normal distribution; consequently all non-normally

distributed values were natural logarithm transformed to better approximate a normal distribution. Mann-Whitney U and Pearson chi-square tests were used to compare continuous and categorical variables, as appropriate. Spearman coefficient was used to evaluate the correlation between variables. Univariate and multivariate logistic regression were used to evaluate the association of biomarkers with peritonitis. Furthermore, we detected the possible collinearity in multivariable analysis through variance inflation factor (VIT), obtaining the factor ≤ 1.6 in all possible combinations of the covariates.

All reported p values were 2-sided, and statistical significance was set at $p < 0.05$. Statistical analysis was performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period, we evaluated 182 patients (91 in the case group and 91 in the control group). No significant differences were found between the 2 groups in terms of age ($p = 0.38$), gender ($p = 0.61$), type of dialysis ($p = 0.33$), dialysis vintage ($p = 0.56$), type of transporter ($p = 0.56$), and Kt/V ($p = 0.46$).

In the case group, we had 80 episodes of peritonitis and 11 cases of suspicious peritonitis without diagnosis of peritonitis (of which 4 with hemoperitoneum and abdominal discomfort; 3 with abdominal pain, diarrhea, and doubtful peritoneal effluent; 3 with cloudy effluent and abdominal discomfort in calcium channel blockers; and 1 with chylous peritoneum).

The clinical patients' characteristics stratified according to the presence of peritonitis are reported in Table 1. Furthermore, in univariate analysis only the $Cl\text{-creat}_w$ was an independent predictor of peritoneal NGAL value ($\beta = -0.004$, $p = 0.003$); but this relationship was lost when we considered the patients with a diagnosis of peritonitis ($\beta = 0.002$, $p = 0.572$).

C-reactive protein, PCT, and peritoneal NGAL had a correlation with WBC in the peritoneal effluent with Spearman's rho of 0,32 ($p < 0.001$), 0,335 ($p < 0.001$), and 0,667 ($p < 0.001$) (Figure 1), respectively.

Table 2 summarizes the data of the univariate and multivariate binary logistic regression in the prediction of peritonitis. In the univariate analysis, all biomarkers were predictors of peritonitis (all p values ≤ 0.001). However, in the multivariate analysis, only Ln WBC count (OR 24.834, $p = 0.012$) and Ln peritoneal NGAL (OR 136.647, $p = 0.01$) were independent predictors of peritonitis events.

The AUC for predicting peritonitis of all biomarkers showed a very good performance for WBC count, and peritoneal NGAL with a value of 0.973 ($p < 0.001$) and

TABLE 1
Clinical Patients' Characteristics in the Whole Cohort and Stratified According to the Presence of Peritonitis

	Peritonitis group Median (IQR)	No peritonitis group Median (IQR)	<i>p</i> value
Patients (number)	80	102	
Age (years)	65 (53.7–73.7)	66.50 (53.25–78)	0.37
Male (%)	77.5	71.6	0.36
CAPD (%)	51.3	69.6	0.12
Diabetes (%)	17.5	35.6	0.07
Hypertension (%)	79.2	86.3	0.21
BMI (kg/m ²)	27.2 (23.8–32)	27.1 (23.9–30.1)	0.62
CRP (mg/dL)	2.1 (0.34–8.9)	0.57 (0.19–1.5)	<0.001
PCT (ng/mL)	0.79 (0.39–1.99)	0.31 (0.21–0.6)	<0.001
Peritoneal NGAL (ng/mL)	192 (117–292)	44.5 (33.25–74)	<0.001
WBC count in peritoneal effluent (10 ⁹ /L)	2.2 (0.88–6.34)	0.02 (0.01–0.05)	<0.001

IQR = interquartile range; CAPD = continuous ambulatory peritoneal dialysis; BMI = body mass index; CRP = C-reactive protein; PCT = procalcitonin; NGAL = neutrophil gelatinase-associated lipocalin; WBC = white blood cell.

Figure 1 — Spearman correlation between WBC and NGAL in peritoneal effluent. 1a: Diagram of correlation between the WBC count in peritoneal effluent and peritoneal NGAL had a Spearman index of 0.667 ($p < 0.01$). 1b: Detail of diagram correlation with the reference line for WBC count in peritoneal effluent and for peritoneal NGAL. WBC = white blood cell; NGAL = neutrophil gelatinase-associated lipocalin; PDE = peritoneal dialysis effluent.

of 0.939 ($p < 0.001$), respectively. Conversely, the AUC was 0.719 ($p = 0.048$) for CRP and 0.754 ($p = 0.042$) for PCT (Figure 2).

On the basis of the AUC in the ROC curve analysis, we fixed the best cutoff at 85 ng/mL. Sensitivity, specificity, false positive, and false negative values for each

TABLE 2
Univariable and Multivariable Logistic Regression for Prediction of Peritonitis

Biomarkers	OR	Univariable analysis		p	Multivariable analysis		p
		95% CI for OR			95% CI for OR		
Ln CRP	1.33	1.12–1.59		0.001	0.271	0.16–1.2	0.084
Ln PCT	2.47	1.62–3.77		<0.001	12.87	0.7–225.3	0.08
Ln WBC	3.98	2.68–5.92		<0.001	24.834	2.1–302.8	0.012
Ln peritoneal NGAL	36.7	12.79–105.6		<0.001	136.647	3.2–5854.2	0.01

OR = odds ratio; CI = confidence interval; CRP = C-reactive protein; PCT = procalcitonin; WBC = white blood cell; NGAL = neutrophil gelatinase-associated lipocalin.

Figure 2 — ROC curve for biomarkers. WBC = white blood cell; NGAL = neutrophil gelatinase-associated lipocalin; CRP = C-reactive protein.

biomarker are summarized in Table 3. Finally, combined tests assumed an interesting behavior: WBC and peritoneal NGAL showed an improvement in terms of specificity (96%) with tolerable reduction of sensitivity (83.7%). Conversely, WBC or peritoneal NGAL showed improvement of sensitivity (98.7%) at the expense of a loss of specificity (67.6%).

DISCUSSION

The present study validated the reliability of peritoneal NGAL as diagnostic marker to predict peritonitis episodes. In our series, peritoneal NGAL was a strong predictor of peritonitis and the test performances of peritoneal NGAL were clinically relevant. In addition,

TABLE 3
Measure of Performance Test with Binary Classification of Peritonitis Biomarkers

	CRP	PCT	WBC in PDE	Peritoneal NGAL
Sensitivity (%)	51	61	91	90
Specificity (%)	65	75.6	93.2	82
False positive (%)	48	24.3	8.6	10
False negative (%)	34	38.3	7	17.6

CRP = C-reactive protein; PCT = procalcitonin; WBC = white blood cell; PDE = peritoneal dialysis effluent; NGAL = neutrophil gelatinase-associated lipocalin.

The test was considered positive if >0.5 mg/dL for CRP, 0.5 ng/mL for Procalcitonin, >0.1 × 10⁹/L for WBC count in peritoneal dialysis effluent, and >85 ng/mL for peritoneal NGAL.

the combined use of WBC and peritoneal NGAL improves the chances of recognizing patients without peritonitis.

Prior studies about NGAL during peritonitis reported a significant increase in the early phase of infection. However, there is a paucity of data available directly concerning its meaning in the diagnosis of peritonitis (14,15). Axelsson *et al.* enrolled patients not in PD with peritonitis recovered in the surgery department (14), whereas Leung *et al.*'s study and Lacquaniti *et al.*'s study were based on only 27 and 30 PD patients (15,16). Finally, we had previously reported on 30 PD patients demonstrating that NGAL had great performance in the diagnosis of peritonitis (17). However, the study evaluated a small cohort of patients and cannot allow definitive conclusions to be made on the role of peritoneal NGAL as a useful biomarker in the early phase of peritonitis. The strengths of this study are a larger number of patients, longer duration, and comprehensive determination of inflammatory markers currently in widespread use for comparison. Furthermore, our

results for qualified markers WBC count, CRP, and PCT were comparable with those reported in previous studies (18,19), an element that increases the validation of our study. Additionally, the present study confirmed our previous reports (20) about the minimal influence of PD features on the level of peritoneal NGAL. Specifically, during peritonitis episodes, we showed how PD did not impact on peritoneal NGAL level.

Finally, peritoneal NGAL correlated strongly with WBC count in peritoneal effluent, but, in some cases, peritoneal NGAL and WBC count in PDE exhibited different behaviors in the early phase of a peritonitis episode. Specifically, in most of the false negative cases, peritoneal NGAL was over the reference range, whereas in most of the false positive cases peritoneal NGAL was in the reference interval. Those observations suggest the specific utility of peritoneal NGAL as a diagnostic tool for peritonitis and its value integrated with WBC count to assist clinicians. Specifically, the concomitant use of WBC and peritoneal NGAL (as both positive tests) allows an interesting improvement of specificity for peritonitis episode; while the concomitant use of WBC or peritoneal NGAL (at least 1 test positive) increases the sensitivity. We believe that the use of WBC and peritoneal NGAL test could be very useful in the clinical setting, allowing a better detection of patients without peritonitis; theoretically its use could reduce incongruous antibiotic treatment. Indeed, we remember the previous studies on WBC count in PDE and its different evaluation about the best cut-off in the diagnosis of peritonitis (3). Specifically, 1 study suggested WBC count in PDE $> 0.2 \times 10^9$ as a cut-off to optimize the specificity of the marker. In this scenario, the use of combined WBC and peritoneal NGAL tests could be extremely interesting when WBC in PDE is under 0.2×10^9 .

Our study has some inherent limitations. It has been previously demonstrated that peritoneal NGAL is influenced by local inflammation (9). The inflammatory state of the peritoneal membrane in basal conditions has been widely demonstrated to complicate research in PD patients. A 4- to 5-fold increase in peritoneal NGAL due to peritonitis could fall in the normal reference values in patients with a very low basal inflammatory state causing false negative results. Conversely, false positive results could be due to increased inflammation of the peritoneal membrane in basal conditions. That confounding factor might be seen to contribute to suboptimal results in terms of sensitivity, specificity, false negative, and false positive values. Recent research into NGAL analysis showed how neutrophils secrete predominantly dimeric NGAL during urinary infections, whereas tubular cells secrete monomeric NGAL under other flogistic stimuli

(21). A topic for future research will inevitably be distinguishing local peritoneal inflammation during peritonitis from baseline local inflammation in the absence of acute peritonitis, for example, by specific evaluation of monomeric and dimeric NGAL ratio in peritoneal effluent. The NGAL assay used to measure peritoneal NGAL was not specifically created for PDE, but currently there is no specific kit for PDE. The development of such a diagnostic tool could aid evaluation of monomeric/dimeric NGAL levels from PDE.

In conclusion, in our study peritoneal NGAL confirmed its usefulness as a marker of peritonitis, especially when it was used in combination with WBC in PDE. Finally, other achievements about reference interval and monomeric/dimeric structure may improve the diagnostic utility.

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DISCLOSURES

Professor C. Ronco has received speaking honoraria from Abbott, Alere, and Gambro. All other authors have no competing financial interests to declare.

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