CLINICAL CHARACTERISTICS AND OUTCOMES OF PERITONEAL DIALYSIS-RELATED PERITONITIS WITH DIFFERENT TRENDS OF CHANGE IN EFFLUENT WHITE CELL COUNT: A LONGITUDINAL STUDY

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◆ **Background:** Effluent white cell count (WCC) is among the important prognostic factors for peritonitis outcome, but its trend has never been studied. We aimed to explore the clinical characteristics and outcomes of peritonitis episodes having different trends in effluent WCC change in the first 5 days.

◆ **Methods:** For each peritonitis episode, we examined the patient's demographic and biochemical data, serial effluent WCC, and organisms cultured. Peritonitis-associated death and transfer to hemodialysis were defined as treatment failure.

◆ **Results:** Based on the trend of effluent WCC in the first 5 days, we divided 190 peritonitis episodes into group A (WCC persistently declined), group B (WCC declined after a transient increase), group C (WCC increased after a transient decline), and group D (WCC persistently increased). In group A, peritonitis was caused mostly by gram-positive organisms, and effluent WCC declined the most quickly, leading to a good prognosis. Although the elevation of effluent WCC was prolonged in group B, and the infections were, compared with those in group A, more often caused by gram-negative organisms, outcomes were not worse. In group C, the effluent WCC was more likely to be higher than 100/ μ L on day 5, and the infection was, compared with those in groups A and B, less likely to be caused by gram-positive organisms. Accordingly, membership in group C independently predicted the worst outcome of peritonitis even adjusted for age, sex, and causative organism.

◆ **Conclusions:** Different trends of change in effluent WCC during the early stage of peritonitis represent different clinical patterns and outcomes. Further investigation for optimizing outcomes is required.

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Peritonitis is a leading cause of mortality and technique failure in peritoneal dialysis (PD) patients (1). Although most of these patients continue on PD uneventfully, catheter removal is required in a subset of them, and some unfortunately die. Thus, it is important to explore prognostic factors related to treatment failure so as to identify high-risk patients as early as possible. Previous studies have found that the absolute effluent white cell count (WCC) on day 3, or its prolonged elevation, is a significant risk factor for an adverse outcome (2–5). The International Society for Peritoneal Dialysis (ISPD) guidelines also recommend that, for patients in whom the effluent fails to clear after 5 days of appropriate antibiotics, management should involve removal of the catheter to conserve the peritoneal membrane for future use (6).

Compared with the absolute WCC in effluent, data on trends of change in the WCC during peritonitis episodes are limited, although the phenomenon was reported in one study more than 10 years ago. As shown in the data obtained by Koopmans *et al.* (7), the peak effluent WCC appears on day 2 in some peritonitis episodes, but on day 1 in others, and the former is associated with impaired peritoneal immune reaction. Chow *et al.* (2) further suspected that it takes 3 days or so for antibiotics to demonstrate an effect on peritonitis.

Thus, we hypothesized that the trend of change in effluent white blood cells (WBCs) might depend on the balance between response to antibiotic therapy and host immune reaction. We were therefore interested

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in exploring how the trend of change in effluent WCC varied in peritonitis episodes, and whether different trends might represent different peritonitis entities and be linked to outcomes in a prospective study. Hopefully, the present study provides prognostic information—additional to the absolute WCC on day 3 or 5—in favor of an early decision to modify the treatment strategy.

METHODS

SUBJECTS

Our study was conducted at the PD center of Peking University First Hospital. All consecutive PD patients who presented with PD-associated peritonitis between 1 January 2008 and 30 June 2011 were recruited. Episodes with at least 1 missing measurement of effluent WCC in the first 5 days were excluded. All patients had received a Tenckhoff catheter and were being dialyzed using continuous ambulatory PD with lactate-buffered glucose dialysate in a twin-bag connection system (Baxter Healthcare, Guangzhou, China). Prophylactic cefazolin had been administered before Tenckhoff catheter placement in most patients. Patients and their caregivers were trained by nurses in the dialysis clinic with a standard initial training program before they were allowed to do exchanges by themselves, as we reported in a previous paper (8).

The study was approved by the medical ethics committee of Peking University. Written informed consent was obtained from each patient.

DIAGNOSIS OF PERITONITIS

All patients at our center were asked to contact us as soon as possible by emergency call when they experienced cloudy effluent or digestive tract symptoms of unknown origin. Each patient had to be assessed by the PD unit nurses and were reviewed by a physician. If peritonitis was suspected, aliquots of PD effluent were sent for cell count (5 mL in an EDTA tube) and bacterial culture (10 mL in a blood culture bottle). Peritonitis was defined as the presence of at least 2 of the following conditions: abdominal pain or tenderness; presence of WBCs (100/mL or more) in peritoneal effluent, with at least 50% polymorphs; and positive effluent culture results (6). In cases in which abdominal pain or tenderness was not present, cloudy fluid combined with at least 1 of the latter 2 conditions was considered diagnostic. The disease severity score was also recorded [calculated as the sum of points for pain (0 = no pain; 1 = moderate pain or nausea not requiring a specific therapy; 2 = severe pain,

usually requiring analgesic therapy, or vomiting; 3 = peritoneal pain with tense abdomen or paralytic bowel, or both) and fever (0 = below 37.5°C; 1 = 37.5°C – 38.9°C; 2 = above 38.9°C)] (9).

BASIC DEMOGRAPHIC AND LABORATORY DATA

Basic demographic and laboratory data were collected prospectively. Each episode of peritonitis was recorded in a separate database, including the patient's age, sex, presence of diabetes at the time of peritonitis, duration of PD before the onset of peritonitis, and the most recent biochemical parameters (such as serum albumin and hemoglobin) measured by automated chemistry analyzer no more than 3 months before the onset of peritonitis.

Examination of the PD effluent included WCC, causative micro-organisms, and drug sensitivities. Patients were instructed to bring the first cloudy fluid to the dialysis center immediately. For each episode of peritonitis, serial WCCs were recorded on days 1 – 5, and on days 7, 14, and 21 after initiation of treatment. Cell counts were obtained by placing an aliquot (5 mL) of effluent immediately into ordinary tubes. Bacterial culture of the PD effluent was performed using the Bactec blood system (BD Biosciences, Franklin Lakes, NJ, USA).

According to the trend of change in effluent WCC during the first 5 days of peritonitis, patients were divided into group A (effluent WCC declined gradually without fluctuation), group B (effluent WCC declined after a transient increase), group C (effluent WCC increased after a transient decline), and group D (effluent WCC persistently increased without fluctuation).

TREATMENT AND FOLLOW-UP

Peritonitis episodes were treated using the standard antibiotic protocol at our center, as modified from the ISPD guidelines (6,10). In general, initial antimicrobial therapy for peritonitis consisted of intraperitoneal administration of a third-generation cephalosporin plus cefazolin (both at a single dose of 1 g once daily). If peritonitis completely resolved during the first 5 days, the standard duration of antibiotic treatment was 2 weeks for *Staphylococcus epidermidis* infection and culture-negative peritonitis, and 3 weeks for other types of bacteria and polymicrobial infection. As suggested by the ISPD guidelines (6), Patients were switched to hemodialysis (HD) and PD catheters were subsequently removed if no improvement was observed after 7 – 14 days of appropriate antibiotic therapy, if the PD effluent grew yeast species or tuberculosis at any time, or if a clinical tunnel infection was diagnosed at the start.

Treatment success was defined as complete resolution of peritonitis (PD effluent WCC < 100/ μ L and clinical resolution) without the need for Tenckhoff catheter removal. Conversely, treatment failure was defined as death attributable to the peritonitis episode or transfer to HD. Death attributable to peritonitis was defined as the death of a patient with active peritonitis or admission with peritonitis or within 2 weeks of a peritonitis episode (10).

STATISTICAL ANALYSIS

The statistical analysis was performed using the SPSS software application (version 13.0 for Windows: SPSS, Chicago, IL, USA). Serial measurements of effluent WBCs were plotted graphically for each group. All data are expressed as mean $\pm$ standard deviation for normally distributed data, and medians with intervals from the 25th to the 75th percentile for skewed data. Categorical variables are expressed as percentages or ratios. Patient data were compared using the chi-square test for categorical variables, an analysis-of-variance F-test for normally distributed continuous variables, and a Mann-Whitney U-test for skewed continuous variables.

It should be noted that, given its small sample size, group D is presented in the data results, but is omitted from the comparisons between groups. Multivariate logistic regression models were built to analyze the predictive role of the trend of change in effluent WCC for risk of peritonitis treatment failure. In model 1, age and sex were included as potential confounders. Then, in model 2, causative organisms [group 1: culture-negative infections and non-*S. aureus* gram-positive infections; group 2: *S. aureus*, gram-negative, and polymicrobial infections (11)] were added to examine if the predictive role of trend of change in effluent WCC was explained by the causative organisms. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. All probabilities were two-tailed, and the level of significance was set at 0.05.

RESULTS

Of 258 peritonitis episodes that occurred between 1 January 2008 and 30 June 2011, 68 had at least 1 missing time point for effluent WCC in the first 5 days and were excluded. Compared with the included episodes, excluded episodes had a higher proportion of peritonitis cases recorded as "pathogen unavailable" (19.1% vs 2.1%, $p < 0.01$) and "pathogen tested negative" (38.2% vs 23.1%, $p = 0.03$). The death rate in the excluded episodes was also relatively higher (16.2% vs 8.4%, $p = 0.07$). All other

clinical characteristics and outcomes were not significantly different between the groups (Table 1).

The remaining 190 episodes were divided into group A ($n = 110$), group B ($n = 61$), group C ($n = 15$), and group D ($n = 4$), according to the trend of change in effluent WCC during the first 5 days of peritonitis (Table 2, Figure 1). In group A, the effluent WCC quickly declined from median of 1822/ μ L and subsequently maintained a level below 100/ μ L after day 3. In group B, effluent WCC increased from a median of 640/ μ L on day 1 to 1492/ μ L on day 2, and thereafter declined. Notably, the effluent WCC was significantly higher in group B patients than in group A patients from day 3 to day 5 (Table 2). The highest effluent WCC on day 1 occurred in group C (median of 2400/ μ L), which declined thereafter, but maintained a high level of 520 – 700/ μ L on days 2 – 4, and then increased again on day 5. In group D, the effluent WCC gradually and continuously increased. The proportion of episodes with an effluent WCC greater than 100/ μ L on day 5 was highest in group C compared with groups B and A (100% vs. 46.8% and 6.5% respectively, $p < 0.01$ for both).

Variables such as sex, a diagnosis of diabetes, body mass index, hemoglobin, serum albumin, total Kt/V, and disease severity score were all nonsignificantly different between group C and groups A and B.

The spectrum of pathogenic bacteria was significantly different between the groups. Group A had the highest rate of gram-positive bacterial infection (77.3% vs 46.3% in group B and 16.7% in group C, both $p < 0.01$) and the lowest rate of gram-negative bacterial infection (15.9% vs 41.5% in group B and 58.3% in group C, both $p < 0.01$). Compared with group C, group B had a higher rate of gram-positive bacterial infection (46.3% vs 16.7%, $p = 0.02$), but a similar rate of gram-negative bacterial infection (41.5% vs 58.3%, $p = 0.73$). The culture-negative rate was lower in group A than in group B (17.8% vs 32.8%, $p = 0.03$), but similar for groups B and C (32.8% and 20% respectively, $p = 0.53$). Table 3 details the results.

In terms of outcome, group C had the highest proportion of all-cause treatment failure (66.7% vs 11.8% in group A and 16.4% in group B, both $p < 0.001$) and the highest death rate (40% vs 5.5% in group A and 4.9% in group B, both $p < 0.001$). In group C, 3 patients experienced ileus, and 1 case of intestinal perforation occurred. A significantly higher proportion of group C patients, compared with group A patients, transferred to HD (26.7% vs 6.4%, $p = 0.03$; Table 4). Groups A and B had similar rates of treatment failure, transfer to HD, and death (all $p > 0.05$). Table 4 details the reasons for transfer to HD and the causes of death.

As can be seen in Table 5, the risk for peritonitis treatment failure was, after adjustment for age and

TABLE 1
Clinical Characteristics of Patients and Peritonitis Outcomes for Included and Excluded Peritonitis Episodes^a

Variable	Peritonitis episodes		<i>p</i> Value
	Included	Excluded	
Patients (<i>n</i>)	190	68	
Age (years)	61.43±12.99	61.08±12.00	0.85
Sex [<i>n</i> (%) men]	72 (37.9)	25 (36.8)	0.87
Diabetes mellitus	88 (46.3)	28 (41.2)	0.47
PD duration (months)	34.90 (14.87–56.45)	34.77 (17.80–56.03)	0.70
BMI (kg/m ²)	23.69±3.79	23.15±4.59	0.35
Hemoglobin (g/L)	106.99±20.20	104.29±20.21	0.65
Serum albumin (g/L)	34.19±5.55	34.56±5.93	0.11
Total weekly Kt/V	1.81 (1.60–2.13)	1.78 (1.61–2.02)	0.91
Weekly RRF	0.15 (0–0.57)	0.28 (0–0.47)	0.62
Causative organism			
Gram-positive	89 (62.2)	21 (61.8)	0.96
Gram-negative	38 (26.6)	10 (29.4)	0.74
Polymicrobial	10 (6.9)	0 (0)	0.11
Tuberculosis	1 (0.7)	0 (0)	1.00
Fungus	3 (2.1)	3 (8.8)	0.13
Culture-negative	43 (23.1)	21 (38.2)	0.03
Untested	4 (2.1)	13 (19.1)	<0.01
Dropouts	35 (18.4)	18 (26.5)	0.16
Transfer to HD	19 (10.0)	7 (10.3)	1.00
Death	16 (8.4)	11 (16.2)	0.07

PD = peritoneal dialysis; BMI = body mass index; RRF = residual renal function; HD = hemodialysis.

^a Data are expressed as mean ± standard deviation for normally distributed variables and median with intervals from the 25th to 75th percentile for skewed variables. Categorical variables are expressed as numbers with percentages or as ratios.

sex, significantly higher for patients in group C than for those in group A [adjusted OR (aOR): 17.41; 95% CI: 4.92 to 61.59; $p < 0.001$] and in group B (aOR: 12.20; 95% CI: 3.26 to 45.45; $p < 0.001$). Even with additional adjustment for causative organisms, patients in group C still had a higher risk of dropout than those in the other two groups (aOR: 13.31; 95% CI: 3.22 to 55.06; $p < 0.001$; and aOR: 8.62; 95% CI: 2.06 to 35.71; $p = 0.003$ respectively). Groups A and B had a similar risk of treatment failure, regardless of additional adjustments for causative organisms.

DISCUSSION

Although the effluent WCC is expected to gradually decline to normal levels within 3 – 5 days after initiation of antibiotic treatment, the change in WCC does not always trend in one direction without fluctuations, as demonstrated by our data. We observed four different trends in effluent WCC change, including a decline without fluctuations (57.9%), a decline after a transient increase

Figure 1 — Different trends of change in the effluent white cell count (WCC) during peritonitis treatment. Group A: a decline in the effluent WCC without fluctuations. Group B: a decline in the effluent WCC after a transient increase. Group C: an increase in the effluent WCC after a transient decline. Group D: a persistent increase in the effluent WCC without fluctuations.

TABLE 2
Demographic and Biochemical Characteristics of Peritonitis Episodes with Different Trends of Change in the Effluent White Cell Count (WCC)^a

Variable	Patient group ^b				<i>p</i> Value ^c		
	A	B	C	D	(A vs B)	(A vs C)	(B vs C)
Patients (<i>n</i>)	110	61	15	4			
Age (years)	61.16±13.20	62.87±12.69	58.27±12.76	58.5 (39–47) ^c	0.41	0.43	0.21
Sex [<i>n</i> (%) men]	43 (39.1)	23 (37.7)	5 (33.3)	1 (25)	0.86	0.67	0.75
Diabetes mellitus [<i>n</i> (%)]	51 (46.4)	27 (44.3)	8 (53.3)	2 (50)	0.79	0.612	0.57
PD duration (months)	38.23 (17.93–59)	29.63 (13.40–49.17)	45.33 (3.18–76.89)	45.33 (14.6–124.1)	0.20	0.64	0.87
BMI (kg/m ²)	23.55±3.99	23.72±3.61	24.21±3.04	25.3 (19.8–31.0) ^d	0.77	0.54	0.63
Hemoglobin (g/L)	106.01±21.90	108.85±16.77	104.7±21.7	105.7 (100.0–118.5) ^d	0.38	0.83	0.43
Serum albumin (g/L)	33.84±5.54	34.60±5.75	34.34±4.87	34.57 (30.7–42.8) ^d	0.40	0.74	0.88
Total weekly Kt/V	1.72 (1.56–2.08)	1.91 (1.62–2.12)	1.88 (1.70–2.26)	2.13 (1.78–2.36)	0.10	0.15	0.74
Weekly RRF	0.16 (0–0.56)	0.13 (0–0.59)	0 (0–0.47)	0 (0–0.22)	0.73	0.71	0.82
Effluent WCC (/μL)							
Day 1	1822 (850–4408)	640 (206–2240)	2400 (1280–4250)	175 (6–2110)	<0.01	0.53	0.01
Day 2	311 (68–935)	1491.5 (332–2890)	630 (215–999)	254 (4–2900)	<0.01	0.25	0.08
Day 3	40 (8–264)	324.5 (112–1720)	700 (113–1920)	800 (300–3500)	<0.01	0.01	0.88
Day 4	12 (2–54)	170 (28–842)	520 (325–3105)	1700 (1220–4500)	<0.01	<0.01	0.04
Day 5	7.5 (2–30)	99 (10–382)	1506 (1000–4625)	2420 (1650–4960)	<0.01	<0.01	<0.01
Day 5>100/μL [<i>n</i> (%)] ^e	5 (6.5)	22 (46.8)	9 (100)	100 (100)	<0.01	<0.01	<0.01
Disease severity score	1 (1–2)	1 (1–2)	1 (1–3)	2 (1–3)	0.71	0.50	0.40

PD = peritoneal dialysis; BMI = body mass index; RRF = residual renal function.

^a Data expressed as means ± standard deviation for normally distributed variables and medians with intervals from the 25th to 75th percentile for skewed variables. Categorical variables are expressed as numbers with percentages or ratios.

^b Group A = episodes in which the effluent WCC declined without fluctuations; group B = episodes in which the effluent WCC declined after a transient increase; group C = episodes in which the effluent WCC increased after a transient decline; group D = episodes in which the effluent WCC persistently increased without fluctuations.

^c Comparisons were not performed between group D (because of its small sample size) and the other groups.

^d Expressed as mean (minimum, maximum).

^e Calculated as the number of episodes with an effluent WCC>100/μL at day 3 or day 5, divided by the total number of episodes in the group.

(32.1%), an increase after a transient decline (7.9%), and a persistent increase without fluctuations (2.1%). The distribution of causative organisms and of peritonitis outcomes was significantly different between the groups.

Our study is the first to explore the clinical characteristics and outcomes of peritonitis episodes with different trends in the change of effluent WCC. Generally, the peak of effluent WCC is supposed to occur on day 1 of peritonitis, as occurred in group A, because host and peritoneal immune responses are activated within several hours of bacterial invasion, with cytokine levels subsequently declining together with bacterial elimination (12–16). However, that pattern was not the case for

group B, whose peak effluent WCC appeared on day 2. Several explanations for that observation are possible. First, a relatively weak peritoneal defense system may result in delayed elevation of the effluent WCC, which is associated with a delayed cytokine response—that is, the maximal cytokine appearance rates occur on day 2, and not on day 1 as indicated in previous studies (7,17). That observation also accords with the subsequent prolonged elevation of WCC. Second, after exposure to antibiotics, bacteria release immunoreactive components such as endotoxins and lipoteichoic acid (18–20), which induce activation of white cells (21). We speculate that the enhanced response to antibiotics observed in group B

TABLE 3
Causative Micro-organisms and Antibiotic Resistance Rates in Peritonitis Episodes with Different Trends of Change in the Effluent White Cell Count (WCC)^a

Variable	Patient group ^b				(A vs B)	p Value ^c	
	A (n=110)	B (n=61)	C (n=15)	D (n=4)		(A vs C)	(B vs C)
Gram-positive organisms	68 (77.27)	19 (46.34)	2 (16.67)	0 (0)	<0.01	<0.01	0.02
<i>Staphylococcus epidermidis</i>	27 (30.68)	4 (9.76)	1 (8.33)	0 (0)	0.01	0.06	1.00
<i>S. aureus</i>	2 (2.27)	2 (4.88)	0 (0)	0 (0)	0.59	1.00	1.00
Other <i>Staphylococcus</i>	19 (21.59)	6 (14.63)	1 (8.33)	0 (0)	0.35	0.29	0.66
<i>Streptococcus</i>	12 (13.64)	2 (4.88)	0 (0)	0 (0)	0.22	0.21	1.00
<i>Enterococcus</i>	6 (6.8)	5 (12.2)	0 (0)	0 (0)	0.31	1.00	0.58
Other	2 (2.27)	0 (0)	0 (0)	0 (0)	1.00	1.00	—
Gram-negative organisms	14 (15.91)	17 (41.46)	7 (58.33)	2 (50)	<0.01	<0.01	0.73
<i>Escherichia coli</i>	6 (6.82)	11 (26.83)	5 (41.67)	1 (25)	<0.01	<0.01	0.63
<i>Klebsiella</i> species	2 (2.27)	3 (7.32)	0 (0)	1 (25)	0.33	1.00	0.56
<i>Pseudomonas aeruginosa</i>	1 (1.14)	1 (2.44)	1 (8.33)	0 (0)	0.54	0.27	0.47
<i>Corynebacterium</i>	3 (3.41)	0 (0)	0 (0)	0 (0)	0.55	1.00	—
<i>Acinetobacter baumannii</i>	2 (2.27)	0 (0)	0 (0)	0 (0)	1.00	1.00	—
Other	0 (0)	2 (4.88)	1 (8.33)	0 (0)	0.10	0.15	1.00
Polymicrobial	5 (5.68)	5 (12.20)	0 (0)	0 (0)	0.20	1.00	0.31
Tuberculosis	0 (0)	0 (0)	1 (8.33)	0 (0)	—	0.15	0.28
Fungus	1 (1.14)	0 (0)	2 (16.67)	0 (0)	1.00	0.06	0.07
Culture-negative	19 (17.76)	20 (32.79)	3 (20)	1 (25)	0.03	0.73	0.53
Pathogen unavailable ^d	3 (2.73)	0 (0)	0 (0)	1 (25)	0.55	1.00	—
Antibiotic resistance rate ^e	29 (36.7)	3 (9.1)	4 (44.4)	1 (50)	0.003	0.72	0.03
For gram-positive	23 (41.4)	3 (17.4)	2 (66.7)	0 (0)	0.09	0.57	0.14
For gram-negative	3 (25.0)	0 (0)	2 (40.0)	1 (50)	0.22	0.60	0.07

^a Data expressed as numbers with percentages.

^b Group A = episodes in which the effluent WCC declined without fluctuations; group B = episodes in which the effluent WCC declined after a transient increase; group C = episodes in which the effluent WCC increased after a transient decline; group D = episodes in which the effluent WCC persistently increased without fluctuations.

^c Comparisons were not performed between group D (because of its small sample size) and the other groups.

^d Dialysate not sent for microbiologic culture. For some patients who live far from our center, only routine tests of effluent were performed at the local hospital before antibiotic therapy was started.

^e Calculated as the number of episodes presenting with antibiotic resistance divided by the total number of bacterial peritonitis episodes in the group. Episodes in which an antibiotic sensitivity test was not performed were excluded (that is, 8 in group A, 3 in group B, 0 in group C, and 0 in group D).

(antibiotic resistance rate of 9.1% vs 36.7% in group A) possibly resulted in the release of immunoreactive components and, thereafter, a higher effluent WCC in response to antibiotics (day 2). Therefore, a transient increase in the effluent WCC occurring in the very early stages of antibiotic treatment (as observed in group B) is not necessarily an indicator of an adverse prognosis, but rather an indicator of a delay in resolution. Third, it is also possible that differences between the groups merely reflect the timing of the initial effluent collection. As Chow *et al.* (2) indicated, the initial effluent collection may not be sufficiently standardized. However, that explanation does not fit with our observations because

the various trends of WCC change were linked with different spectra of causative organisms, obviously suggesting distinct clinical entities in the various groups. Notably, compared with group A, group B seemed to have a higher proportion of infections with gram-negative bacteria, which raises the question of whether an early adjustment to the antibiotic regime should be made based on this interesting clue in effluent WCC trends.

The “U” shape of the effluent WCC trend in group C is possibly related to an interaction between the bacteria present and the response to antibiotics. Earlier studies found that a large quantity of bacteria is usually associated with unsuccessful bacterial elimination, with

TABLE 4
Treatment Failure for Peritonitis Episodes with Different Trends of Change in the Effluent White Cell Count (WCC)

Variable	Patient group ^a				(A vs B)	p Value ^c	
	A (n=110)	B (n=61)	C (n=15)	D (n=4)		(A vs C)	(B vs C)
Treatment failure [n (%)]	13 (11.8)	10 (16.4)	10 (66.7)	2 (50)	0.48	<0.001	<0.001
Transfer to hemodialysis (HD) [n (%)]	7 (6.4)	7 (11.5)	4 (26.7)	1 (25)	0.24	0.03	0.13
Major reasons contributing to transferring to HD							
Ultrafiltration failure	0	1	0	0	0.36	—	1.00
Prolonged elevation of effluent WCC	7	5	3	1	0.65	0.10	0.07
Sepsis	0	1	0	0	0.36	—	1.00
Fungal infection	0	0	1	0	—	0.12	0.20
Death [n (%)]	6 (5.5)	3 (4.9)	6 (40)	1 (25)	1.00	<0.001	<0.001
Major complications contributing to death							
Sepsis	0	2	6	0	0.12	<0.001	0.001
Cardiovascular accident	3	1	0	1	1.00	1.00	1.00
Pulmonary infection	1	0	0	0	1.00	1.00	—
Severe malnutrition	1	0	0	0	1.00	—	—
Gastrointestinal bleeding	1	0	0	0	1.00	—	—

^a Group A = episodes in which the effluent WCC declined without fluctuations; group B = episodes in which the effluent WCC declined after a transient increase; group C = episodes in which the effluent WCC increased after a transient decline; group D = episodes in which the effluent WCC persistently increased without fluctuations.

^c Comparisons were not performed between group D (because of its small sample size) and the other groups.

TABLE 5
Risk and Adjusted Risk of Peritoneal Dialysis (PD) Dropout in Peritonitis Episodes with Different Trends of Change in the Effluent White Cell Count (WCC)

Variable ^a	Model 1		Model 2	
	aOR (95% CI)	p Value	aOR (95% CI)	p Value
Changing trend of effluent WCC				
Group A	Reference		Reference	
Group B	1.43 (0.58 to 3.51)	0.44	1.54 (0.60 to 3.99)	0.37
Group C	17.41 (4.92 to 61.59)	<0.001	13.31 (3.22 to 55.06)	<0.001
Group B	Reference		Reference	
Group C	12.20 (3.26 to 45.45)	<0.001	8.62 (2.06 to 35.71)	0.003
Age	1.02 (0.99 to 1.06)	0.18	1.03 (0.99 to 1.07)	0.10
Sex	1.48 (0.64 to 3.43)	0.36	1.96 (0.81 to 4.76)	0.14
Causative organism				
Non- <i>Staphylococcus aureus</i> , gram-positive cocci and culture-negative	—	—	Reference	
<i>S. aureus</i> , gram-negative and polymicrobial	—	—	1.77 (0.71 to 4.42)	0.22

aOR = adjusted odds ratio; CI = confidence interval.

^a Group A = episodes in which the effluent WCC declined without fluctuations; group B = episodes in which the effluent WCC declined after a transient increase; group C = episodes in which the effluent WCC increased after a transient decline; group D = episodes in which the effluent WCC persistently increased without fluctuations.

bacterial numbers initially declining, but subsequently persistently increasing (22). Compared with the other two groups, group C patients might have been exposed to a larger quantity of bacteria, and thus it is unsurprising that many patients in group C died from complications of sepsis. Furthermore, it is well known that certain organisms, particularly gram-negative organisms, typically undergo genetic mutation, with selection pressure for beta-lactamase-producing mutants (23), thus becoming resistant to cephalosporins. Of the 12 culture-positive peritonitis episodes in group C, 7 were reported to produce beta-lactamase, with 5 being identified as *Enterobacter*, 1 as *Pseudomonas*, and 1 as *Edwardsiella tarda* (23). We cannot exclude the possibility that the U-shaped trend of WBCs might point toward a potentially inducible resistance to antibiotics when an initial response is followed by deterioration. Further studies with larger sample sizes are therefore needed to explore whether, for peritonitis with an initial dip of effluent WCC, attention should be given to intensifying antibiotic treatment for gram-negative bacteria and investigating for potential intestinal diseases, with a more intensive follow-up frequency and more prompt catheter removal.

There are limitations to the present study. First, peritonitis episodes with missing data during the first 5 days were excluded, possibly resulting in selection bias. Although clinical characteristics were not significantly different between the included and excluded episodes, the excluded episodes were associated with a relatively higher death rate (16.2% vs 8.4%, $p = 0.07$). Our results should therefore be further verified by well-designed cohort studies with a larger sample size. Second, the small sample size in this study, particularly in groups C and D, prevented an adequate subgroup analysis, and thus the ability to draw definitive conclusions from our data is limited. Third, the overall proportion of culture-negative peritonitis (22.6%) exceeds the ISPD recommendation (6), particularly in group B (33%), which may affect interpretation of the data relating to the causative microorganisms. The single-center design of this study also affects the generalizability of our findings. In addition, we have no data on the quantity and virulence of the pathogenic organisms and the potency of the peritoneal and host defense systems, which means that the present study design could not explore potential mechanisms for the different trends of change in the effluent WCC and their association with peritonitis outcomes.

CONCLUSIONS

Our study demonstrates for the first time that different trends of change in effluent WCC reflect different

spectra of organisms and different peritonitis outcomes. A transient early increase in the effluent WCC is possibly a sign of delayed resolution, but not worse outcome. By contrast, an increase after a transient decline in the effluent WCC is associated with a significantly higher risk of treatment failure. Because those two trends were more often associated with gram-negative organisms, an exploration of whether intensifying the specific antibiotic treatment for gram-negative bacteria should be applied in these cases is justified. Our findings are of value for estimating the causative organism and choosing an optimized strategy for the treatment of peritonitis.

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All authors read and approved the final manuscript.

DISCLOSURES

No financial conflicts of interest exist.

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