

# Circulating Mediators and Organ Function in Patients Undergoing Planned Relaparotomy vs Conventional Surgical Therapy in Severe Secondary Peritonitis

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**Hypothesis:** Planned relaparotomy (PRL) has been suggested to have detrimental effects on the systemic activation of inflammation mediators, thereby enhancing organ dysfunctions as assessed by clinical scores in secondary peritonitis.

**Design:** Prospective, nonrandomized control trial.

**Setting:** Intensive care units of an urban and a university teaching hospital.

**Patients:** Twenty-nine patients with secondary peritonitis.

**Interventions:** Of the 29 patients with comparable initial peritonitis conditions, 11 underwent PRL and 18 obtained primary abdominal closure. Blood samples were obtained preoperatively and at 2, 6, 8, 12, 18, 24, 30, 36, 42, and 48 hours after the primary operation, then every 12th hour until day 5 and once daily until day 8.

**Main Outcome Measures:** Quantification of circulating inflammation parameters (coagulation, acute-phase proteins, cytokine system, cell adhesion, opsonization) in correlation with Acute Physiology and Chronic Health

Evaluation II, multiple organ failure, and Sepsis-Related Organ Failure Assessment scores.

**Results:** Preoperatively, the patient groups did not differ in mean age, cause of peritonitis, or clinical scores. On average, 5.1 (SEM,  $\pm 0.7$ ; range, 3-11) lavage treatments were performed in the PRL group, with 90% of the procedures executed during the first 6 days. The PRL treatment resulted in a significantly higher need of blood components and an increased inflammation mediator response, especially concerning coagulation factors, proinflammatory cytokines, adhesion molecules, and opsonic parameters. During PRL, clinical score systems showed higher values and a delayed decline compared with primary abdominal closure treatment. Incidence of multiorgan failure, mortality, and the mean intensive care unit hospitalization period were clearly more pronounced in the PRL group.

**Conclusion:** In our pilot study, additional lavage treatment of secondary peritonitis resulted in an enhancement of systemic inflammatory mediator response (in particular interleukin 8), which may contribute to a further impairment of organ function.

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**I**MPROVED pathophysiological understanding in general and advances in surgical intensive care medicine in particular have resulted during the past years in more aggressive therapy of severe diffuse peritonitis.<sup>1-6</sup> The standard method of “on demand” relaparotomy, closed postoperative lavage methods, and different lavage variants of open and semiopen treatment of the abdominal cavity are currently in competition. Nevertheless, more than 80% of all peritonitis cases can be successfully

treated with the standard method.<sup>7,8</sup> Indications for applicability and duration of a chosen therapy have so far been made solely based on clinical criteria and the experience of the surgical department. Controlled prospective studies on the different interventional procedures are not available.

Additional operations potentially expose even well-monitored patients to the risk of postoperative hemodynamic impairment with subsequent global or regional hypoperfusion.<sup>9</sup> Sauter et al<sup>10</sup>

## PATIENTS AND METHODS

### SELECTION AND TREATMENT OF PATIENTS

After informing the attending physicians about the protocol, 29 adult patients who exhibited signs of severe peritonitis (temperature,  $>38^{\circ}\text{C}$ ; leukocyte level,  $>10 \times 10^3/\mu\text{L}$  or  $<3 \times 10^3/\mu\text{L}$ ; and  $>2$ -quadrant peritonitis) were prospectively included in the study, which was conducted between December 1994 and February 1995 and November 1996 and January 1997 (Departments of Surgery of the Central Hospital in Augsburg, Germany, and of the University of Munich, Munich, Germany). During both periods all patients who fulfilled the criteria entered the study. All 29 patients had comparable initial conditions (early intervention, source control, and intraoperative lavage). Of these 29 patients, 11 underwent PRL and 18 obtained primary abdominal closure (PAC). Prewarmed ( $37^{\circ}\text{C}$ ) Ringer lactate solution (Fresenius, Erlangen, Germany) was used for lavage (10-15 L each time).

The classic staged lavage in the PRL group with scheduled relaparotomy after primary intervention involved a temporary wound closure using a zipper dressing made of polyester tissue coated with polyethylene on both sides (Ethizip; Ethicon, Norderstedt, Germany). The Ethizip was changed after 2 to 3 days. The lavage frequency was normally once every 24 hours within the first postoperative week. When the abdominal cavity was found to be clean (clear exudate, granulation tissue, germ-free microbiologic smear), the abdominal wall was closed.

Primary intervention was scheduled in the PAC group after the initial source was controlled, the abdominal cavity was cleaned (laved), and drainages were applied. The design of the study was such that an additional operation would have been considered if local complications or general signs of sepsis persisted or reoccurred. In the case of a nonscheduled relaparotomy demanding staged lavage treatment within the first 7 postoperative days, the patient would have been excluded from the study.

In general, all patients were treated according to the hospitals' guidelines for peritonitis care. Following primary intervention with source control and subsequent lavage, patients' treatment was continued in the surgical intensive care unit (ICU), including monitoring, mechanical ventilation (if required), and circulatory support. According

to our standard procedure, all patients had abdominal drains. Sedation was achieved with fentanyl citrate and midazolam hydrochloride; ranitidine hydrochloride was given to prevent stress ulcer, and intravenous high-molecular-weight sodium heparin (4 IU/kg of body weight per hour) was administered routinely. Use of the heparin was started 6 hours postoperatively. Antibiotic therapy was started with a combination of a second-generation cephalosporin and metronidazole. Selective intestinal decontamination was performed in all patients. Blood components, including fresh frozen plasma, individual coagulation factors, or mixtures (eg, PPSB [factor II, prothrombin; factor VII, proconvertin; factor X, Stuart-Prover factor; and factor IX, anti-hemophilia factor B]), were given specifically in case of clotting disturbances. Platelets were supplied when hemorrhage occurred owing to thrombocytopenia. Packed red blood cells were reserved for anemia with cardiovascular instability and severe hypovolemia. Patients were nourished parenterally with glucose and amino acid solutions and fatty acids. A change to enteral diet was carried out after the fifth day or after the onset of intestinal activity. The study was approved by the institutional review boards of both hospitals. Informed consent was given by all patients.

### PERIODS OF INVESTIGATION AND SAMPLE PREPARATION

Clinical and routine laboratory parameters were monitored immediately before and after the operation (2 hours after abdominal wall closure) and daily at 8 AM during an 8-day observation period. Arterial blood samples for estimation of inflammation parameters were obtained preoperatively and 2, 6, 8, 12, 18, 24, 30, 36, 42, and 48 hours postoperatively and thereafter every 12th hour until day 5 and once daily until day 8. The blood samples were processed to citrated plasma or serum and centrifuged at 4000 rpm for 15 minutes at  $10^{\circ}\text{C}$ . The supernatants were deep frozen in aliquots at  $-70^{\circ}\text{C}$  until assayed.

### ANALYSIS OF PERITONITIS SEVERITY, MICROBIOLOGY, ORGAN FAILURE, AND GENERAL LABORATORY PARAMETERS

Initial severity of peritonitis was judged according to the Mannheim Peritonitis Index.<sup>12</sup> Reduction and/or persistence of

Continued on next page

demonstrated recently that reoperation trauma induces an early postoperative rise in interleukin (IL) 6 levels and that systemic cytokine release and hemodynamic instability may be associated with reoperation trauma. Long-term observations of other mediator responses are lacking and are, therefore, investigated in the present study. Although analysis of the rinsing liquid from the peritoneal cavity shows effective elimination of inflammation mediators, endotoxin, and other particles,<sup>2,11</sup> we hypothesize that additional manipulations involved in planned relaparotomy (PRL) of the inflamed peritoneum may not only cause local irritation but also promote further manifestations of a systemic inflammatory response by releasing various mediators into the circulation with the capability of organ function impairment.

## RESULTS

### ADMISSION DATA, OUTCOMES, AND CLINICAL FOLLOW-UP OF ORGAN FAILURE

Demographic and clinical data of the patients and distribution with regard to cause, origin, and bacterial spectrum of the peritonitis in both treatment groups are given in **Table 1** and **Table 2**. Although some minor group deviations existed, no statistically significant differences were obvious. Specimens obtained intraoperatively from the abdominal cavity exudate showed growth of pathogens in 24 patients. Cultures positive for *Escherichia coli* and bacteroides were seen in 5 PRL patients (46%) and 6 PAC subjects (33%). *Candida albicans* was

organ dysfunctions was determined using the Acute physiology and Chronic Health Evaluation II (APACHE II), multiple organ failure (MOF), and Sepsis-related Organ Failure Assessment (SOFA) scores.<sup>13-15</sup>

Results of the microbiologic analysis are given for the first intervention only. Leukocyte and thrombocyte counts, bilirubin level, creatinine level, PaO<sub>2</sub>/fraction of inspired oxygen (FiO<sub>2</sub>) quotient, partial thromboplastin time (PTT), and prothrombin time (PT) were determined by routine methods.

#### SPECIAL BIOCHEMICAL INFLAMMATION PARAMETERS

##### Coagulation Parameters

Prothrombin fragment 1+2 and thrombin-antithrombin III (TAT) complex, as indicators of coagulation activation, were determined with a sandwich immunoassay technique (Enzygnost F1+2 and TAT; Behringwerke, Marburg, Germany) (plasma standard range: F1+2, 0.44-1.10 nmol/L; TAT complex, 1.0-4.1 ng/mL). Latent thrombin activity (prothrombin) was measured in citrated plasma (standard range, 80%-125%) using a specific chromogenic substrate test (S-2238; Haemachrom Diagnostica GmbH, Essen, Germany). The quantitative determination of soluble thrombomodulin was achieved with a sandwich enzyme-linked immunosorbent assay (ELISA; Diagnostica Stago, Paris, France) (plasma standard range, 16.8-42.6 ng/mL).

##### Acute-Phase Reactants

C-reactive protein (plasma standard range, <0.5 mg/dL) was determined with radial immunodiffusion using LC partigen plates (Behringwerke). The infection-associated procalcitonin (plasma standard range, <0.5 µg/L) was quantified with an immunoluminometric assay (Brahms Diagnostica GmbH, Berlin, Germany).

##### Parameters of the Cytokine System

The IL-1 receptor antagonist levels (serum standard range, 157-3170 pg/mL) were determined quantitatively using a

sandwich ELISA (Amersham, Braunschweig, Germany). The IL-6 (serum standard range, 0-6 pg/mL) and IL-8 (serum standard range, 0-30 pg/mL) levels were also quantified with sandwich ELISAs (R & D Systems, Abingdon, Oxon, England).

##### Parameters of Opsonization

The opsonin's IgG (plasma standard range, 800-1800 mg/dL) and C3 complement (plasma standard range, 56-120 mg/dL) levels were determined with radial immunodiffusion using LC partigen plates (Behringwerke). The opsonization capacity (mainly comprising IgG and C3) was detected by a chemiluminescence measurement (modified according to Billing et al<sup>16</sup>) in highly diluted normal donor blood after activation of the phagocytes with zymosan that was preopsonized with patient serum. The activity was expressed as a percentage of a standard serum.

##### Soluble Adhesion Molecules

Concentrations of the following parameters in serum were quantified with specific sandwich ELISAs (Bender MedSystems, Vienna, Austria): L-selectin (standard range, 487-1096.3 ng/mL), P-selectin (standard range, 111-266 ng/mL), and intercellular adhesion molecule 1 (standard range, 180-280 ng/mL).

##### Parameters of Organ Function

For the quantitative determination of procollagen III peptide (P-III-P; plasma standard range, 0.3-0.8 E/mL) a radioimmunoassay was applied using the principle of a 2-stage sandwich test (CIS Diagnostik GmbH, Dreieich, Germany). Neopterin concentration (serum standard range, 1-10 nmol/L) was determined with a radioimmunoassay (Hening, Berlin, Germany).

##### STATISTICAL ANALYSES

Data are given as mean ± SEM (Wilcoxon *U* test). The Pearson  $\chi^2$  test was used as appropriate. Significance was accepted at  $P \leq .05$ . All statistical calculations were performed using a statistical computer program (SPSS version 10.0; SPSS Inc, Chicago, Ill).

isolated only in the PAC group. The portion of malignant tumors was lower and part of the colon and rectum perforation was higher in the PRL patients.

On average, 5.1 ± 0.7 staged lavages (range, 3-11) were performed in the PRL group, with 90% of them being executed within the first 6 days after the primary operation. In the PAC group, no additional operation was necessary.

Concerning judgment of severity of peritonitis and organ failure, the mean values of study admission data of the Mannheim Peritonitis Index and APACHE II score were equal in both groups, whereas the MOF and SOFA scores showed higher (yet not statistically different) values for patients who underwent PRL (**Table 3**).

The in-hospital mortality was 21% for the entire cohort (6/29), 27% in the PRL group (3/11), and 17% in the PAC group (3/18). The cause of death in all cases was

intractable MOF owing to the underlying abdominal sepsis. A significant difference was found with respect to the time of death: patients in the lavage group died significantly later than patients with PAC (PRL group, 17.7 ± 0.7 days; PAC group, 5.7 ± 3.7 days;  $P = .02$ ).

The mean period of ICU hospitalization for the PRL group was significantly longer (33.3 ± 7.2 days) than for the PAC group (4.9 ± 0.8 days;  $P < .001$ ). Disregarding nonsurvivors (3 in each group), the deviation was significant (PRL group, 27.5 ± 7.3 days; PAC group, 4.1 ± 0.6 days;  $P = .001$ ).

Although the course of the PaO<sub>2</sub>/FiO<sub>2</sub> quotient as an indicator of lung function was only slightly lower in the PRL group during the entire study period (**Figure 1**), the mean number of days with mechanical ventilation showed significant group differences (PRL group, 14.5 ± 2.0 days; PAC group, 3.3 ± 0.7 days;  $P < .001$ ). A sig-

**Table 1. Preoperative Characteristics, Number of Lavages, and In-Hospital Mortality of Patients With Peritonitis Stratified Into Planned Relaparotomy (PRL) Treatment or Primary Abdominal Closure (PAC) Groups**

Parameter	PRL (n = 11)	PAC (n = 18)	P Value
Age, mean (SEM), y	56.9 (3.8)	63.7 (3.9)	.1*
Sex, F/M	5/6	12/6	.5†
Malignant tumor, yes/no	2/9	9/9	.2†
No. of lavages, mean (SEM)	5.1 (0.7)	1	<.001*
Death, yes/no	3/8	3/15	.8†

\*Wilcoxon U test.  
†Pearson  $\chi^2$  test.

**Table 2. Cause, Origin, and Primary Bacterial Spectrum in Patients With Peritonitis Stratified Into Planned Relaparotomy (PRL) Treatment or Primary Abdominal Closure (PAC) Groups\***

	Total (N = 29)	PRL (n = 11)	PAC (n = 18)
<b>Cause</b>			
Inflammation	10 (35)	4 (36)	6 (33)
Ischemia	5 (17)	2 (18)	3 (17)
Anastomosis leakage	9 (31)	4 (36)	5 (28)
Traumatic or iatrogenic	2 (7)	0	2 (11)
Tumor perforation	3 (10)	1 (9)	2 (11)
<b>Origin</b>			
Colon and rectum	15 (52)	8 (73)	7 (39)
Jejunum or ileum	6 (21)	2 (18)	4 (22)
Stomach or duodenum	6 (21)	1 (9)	5 (28)
Other	2 (7)	0	2 (11)
<b>Bacterial spectrum</b>			
Aerobic	8 (28)	4 (36)	4 (22)
Aerobic and anaerobic	14 (48)	6 (55)	8 (44)
<i>Candida albicans</i>	2 (7)	0	2 (11)
None	5 (17)	1 (9)	4 (22)
<i>Escherichia coli</i>			
Without bacteroides	18 (62)	6 (55)	12 (67)
With bacteroides	11 (38)	5 (46)	6 (33)

\*Data are presented as number of affected patients and distribution (percentage) within the groups.

nificant difference was also obvious only for surviving patients of both groups (PRL group, 14.6 ± 2.8 days; PAC group, 2.9 ± 0.5 days;  $P < .001$ ).

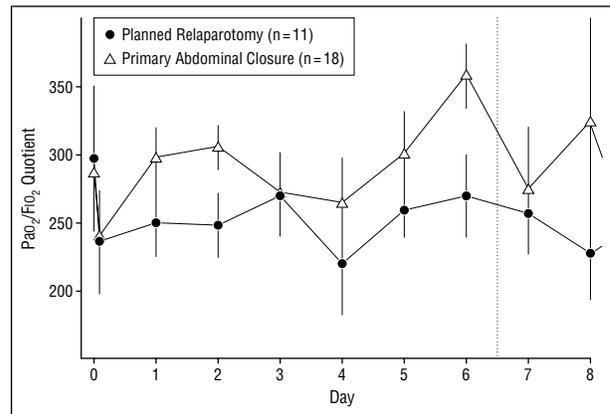
As depicted in **Figure 2**, the course of the APACHE II score was similar in the 2 treatment groups, whereas the MOF and SOFA scores exhibited significantly higher values in the PRL group. Thus, the mean values of the MOF score amounted to 5.2 ± 0.6 in the PRL group and 2.6 ± 0.3 in the PAC group throughout the 8-day observation period ( $P = .001$ ). The respective values of the SOFA score were 8.3 ± 0.8 and 4.7 ± 0.6 ( $P = .003$ ).

Patients undergoing planned additional operations needed more blood product transfusion (erythrocyte concentrates, 13.3 ± 5.2 for the PRL group vs 3.9 ± 0.6 for the PAC group,  $P = .02$ ; fresh frozen plasma (U = 250 mL), 26.6 ± 10.1 U for the PRL group vs 8.5 ± 2.1 U for the PAC group,  $P = .03$ ). Moreover, thrombocyte concentrates (U = 200 mL) were required only in patients undergoing additional lavages (8.7 ± 7.2 U for the PRL group).

**Table 3. Intraoperative Value of Mannheim Peritonitis Index (MPI) and Preoperative Values of Acute Physiology and Chronic Health Evaluation II (APACHE II), Multiple Organ Failure (MOF), and Sepsis-related Organ Failure Assessment (SOFA) Scores of Patients With Peritonitis Stratified Into Planned Relaparotomy (PRL) Treatment or Primary Abdominal Closure (PAC) Groups\***

Score	PRL (n = 11)	PAC (n = 18)	P† Value
MPI	30.5 (1.8) [21-38]	27.5 (1.5) [16-37]	.12
APACHE II	14.0 (1.1) [8-20]	15.0 (1.7) [5-25]	.83
MOF	5.2 (0.9) [1-10]	4.0 (0.9) [1-8]	.08
SOFA	5.2 (0.9) [3-12]	3.1 (0.6) [1-7]	.07

\*Data are presented as mean (SEM) [range].  
†Wilcoxon U test.

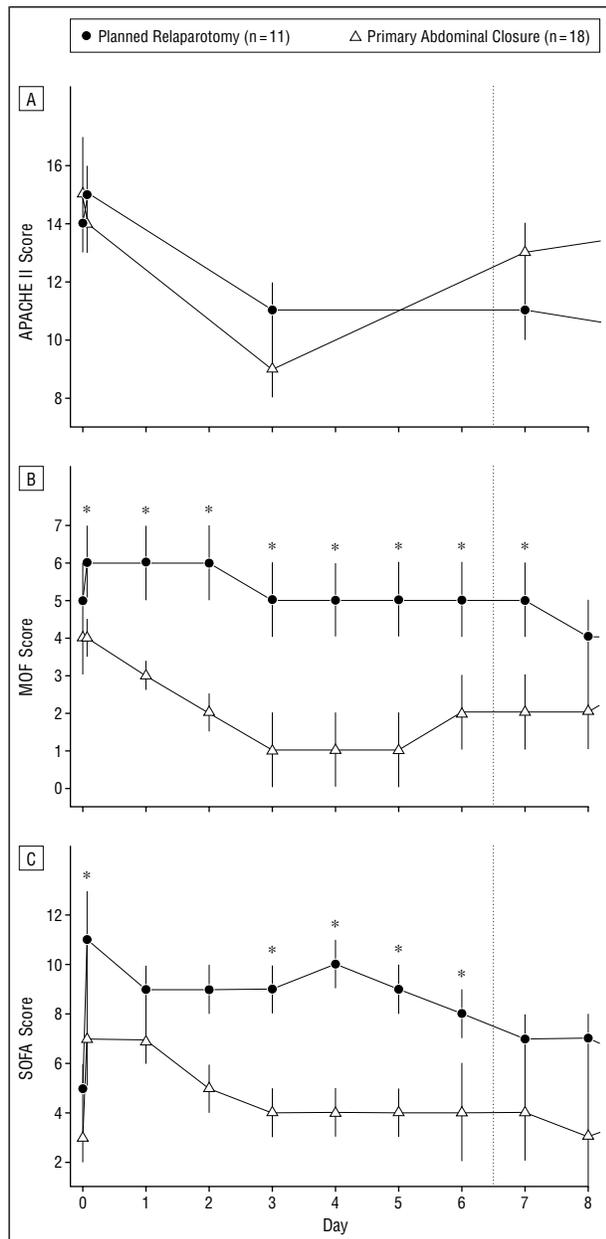


**Figure 1.** Mean PaO<sub>2</sub>/fraction of inspired oxygen (F<sub>i</sub>O<sub>2</sub>) quotients in patients with peritonitis. Error bars indicate SEM; dashed line, end of planned relaparotomy period.

## COAGULATION PARAMETERS

The routine laboratory coagulation parameters PTT and PT were pathologically elevated (mean, 42.2 seconds) and reduced (mean, 71.5%), respectively, to the same extent in both patient collectives throughout the entire study period (data not shown). In contrast, the thrombocyte count in whole blood was slightly lower in the lavage group at the beginning of the study. During the following observation period, particularly within 3 days after completion of the primary lavage, the mean thrombocyte cell count in the PRL group showed significantly diminished values compared with the PAC group (**Figure 3**).

During the first 6 days of observation, the latent thrombin activity of prothrombin in the plasma of the PRL group exhibited on average negligibly lower values (data not shown), whereas the prothrombin fragment 1 + 2 was significantly elevated compared with the PAC subjects (Figure 3), thus indicating the persistently higher activation of coagulation (4.4 ± 0.7 nmol/L for the PRL group and 2.8 ± 0.4 nmol/L for the PAC group;  $P = .04$ ). This was further confirmed by the nearly identical pathological plasma concentration pattern of the TAT complex. Although the elevation was more pronounced in the PRL group during the lavage period, no statistically



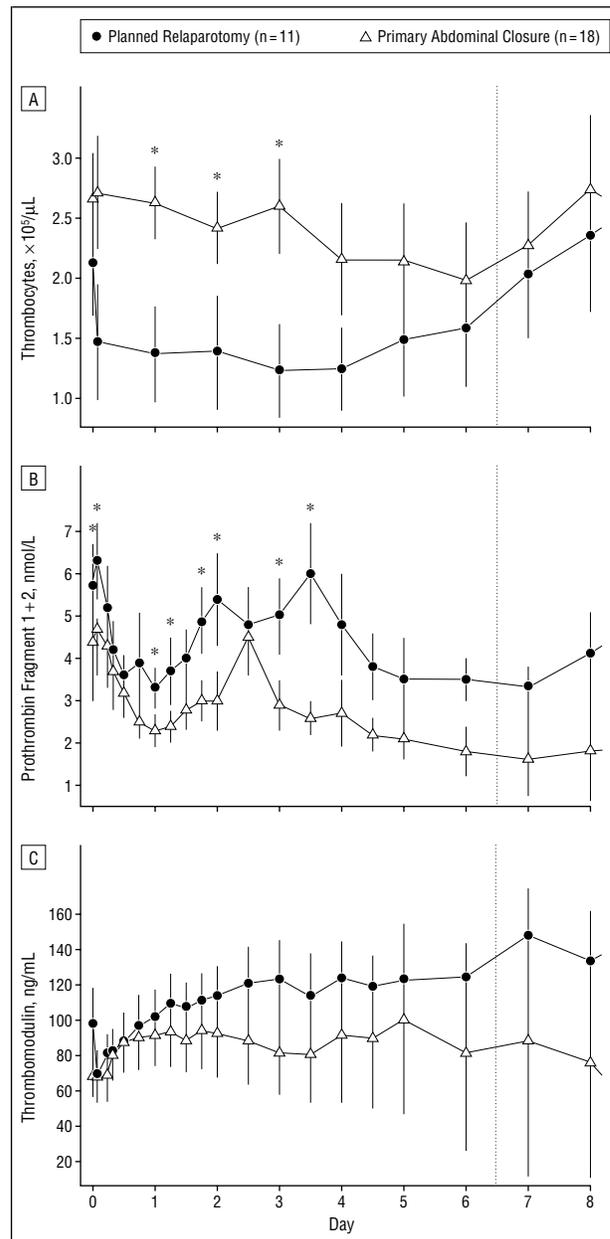
**Figure 2.** Acute Physiology and Chronic Health Evaluation II (APACHE II) (A), multiple organ failure (MOF) (B), and Sepsis-related Organ Failure Assessment (SOFA) (C) scores in patients with peritonitis. Error bars indicate SEM; asterisk, Wilcoxon *U* test,  $P < .05$ ; and dashed line, end of planned relaparotomy period.

significant difference between PRL and PAC subjects could be evaluated (data not shown).

In contrast, the solubilized form of the endothelial thrombin-binding protein thrombomodulin in plasma demonstrated significantly higher values in the PRL group (Figure 3) during the lavage period and in the continued course of the observation period (days 1-6:  $115.5 \pm 16.5$  ng/mL for the PRL group vs  $86.6 \pm 17.3$  ng/mL for the PAC group;  $P = .05$ ).

#### LEUKOCYTES AND ACUTE-PHASE PROTEINS

In both study groups, the leukocyte count showed a continual increase after an immediate decline following the

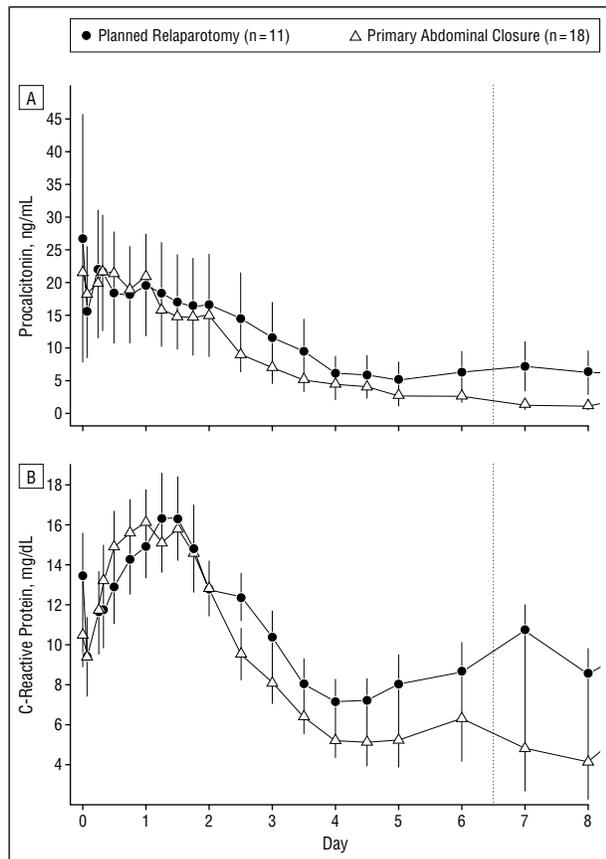


**Figure 3.** Thrombocyte count (A), prothrombin fragment 1+2 (B), and thrombomodulin (C) in the circulation in patients with peritonitis. Error bars indicate SEM; asterisk, Wilcoxon *U* test,  $P < .05$ ; and dashed line, end of planned relaparotomy period.

intervention. No significant differences prevailed at any time. A similar discrimination applied to the plasma level of the C-reactive protein, although the decline in concentration proceeded somewhat more rapidly in the PAC group and approximated the baseline range at an earlier stage (Figure 4). Likewise, the preoperative procalcitonin plasma values of the PRL group were moderately elevated above those of the PAC patients during the lavage and throughout the entire observation period (Figure 4).

#### PARAMETERS OF THE CYTOKINE SYSTEM

The serum pattern of the cytokines showed a comparable picture for IL-1 receptor antagonist (ra), IL-6, and



**Figure 4.** Procalcitonin (A) and C-reactive protein (B) in the circulation in patients with peritonitis. Error bars indicate SEM; asterisk, Wilcoxon *U* test,  $P < .05$ ; and dashed line, end of planned relaparotomy period.

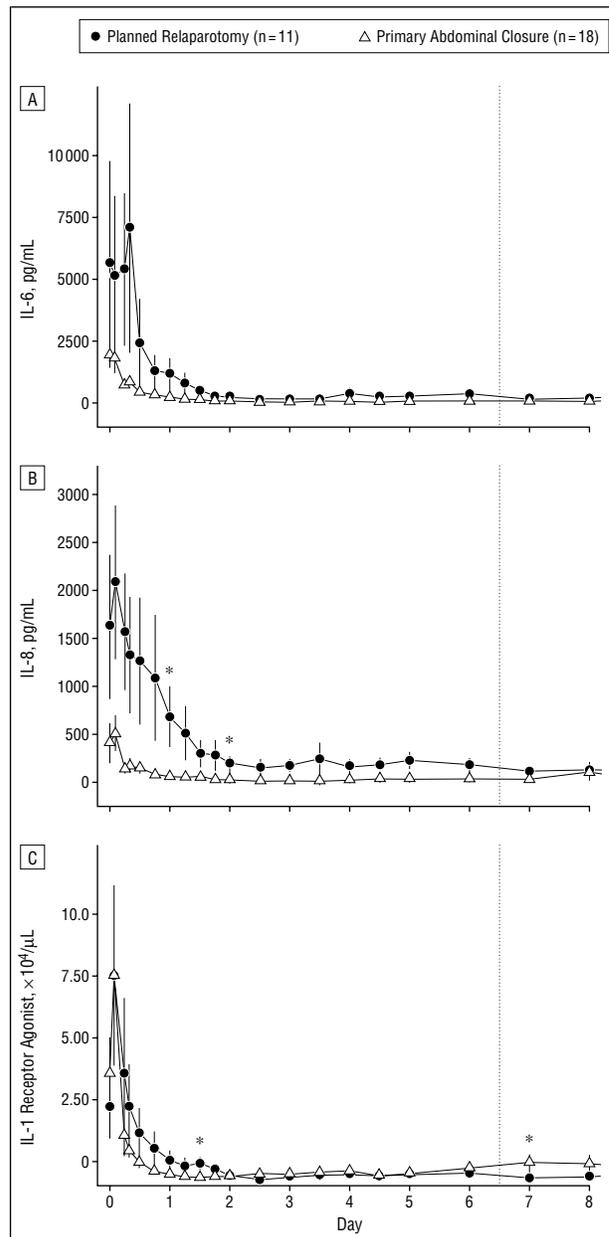
IL-8, with initially high values reaching their maximum at the early postoperative stage followed by a steep decrease within the next 2 days. Although all cytokine concentrations were clearly higher in the PRL group (Figure 5), a significant difference was found only for IL-8 in the early postoperative phase.

#### PARAMETERS OF OPSONIZATION

The IgG plasma values showed no group-related difference, whereas the C3 values of the PRL group stayed consistently below those of the PAC subjects. In conformity with the latter, the mean values of the serum opsonization capacity (percentage of the standard serum) were significantly lower in the PRL group during the first days of additional lavages (Figure 6).

#### PARAMETERS OF CELL ADHESION

Soluble L-selectin and P-selectin in serum as measures of the activation of granulocytes, thrombocytes, and endothelial cells were on average higher in the PAC group than in the PRL group, whereas the mean intercellular adhesion molecule 1 values indicative of an overall cell activation showed an inverse pattern (Figure 7). However, no significant group differences were apparent for any of the soluble adhesion molecules.

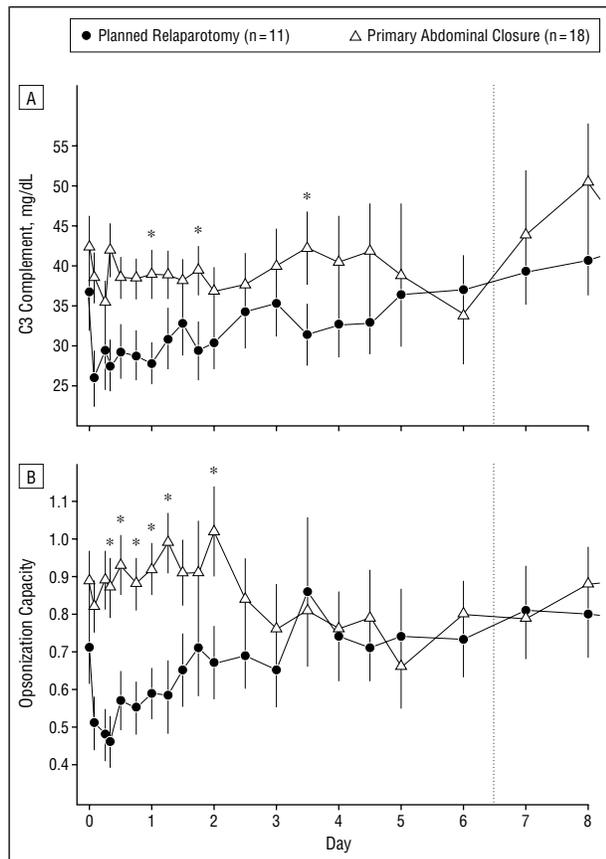


**Figure 5.** Parameters of the cytokine system (interleukin [IL] 6 [A], IL-8 [B], IL-1 receptor antagonist [C]) in the circulation in patients with peritonitis. Error bars indicate SEM; asterisk, Wilcoxon *U* test,  $P < .05$ ; and dashed line, end of planned relaparotomy period.

#### PARAMETERS OF VARIOUS ORGAN FUNCTIONS

As an indication of the impaired eliminatory function of the liver, values of circulating P-III-P were significantly higher during the lavage phase and continued to rise after the end of the lavage period in the PRL group (Figure 8). Similarly, serum bilirubin levels remained significantly higher in the PRL group especially from day 3 to day 5 of the observation period (Figure 8).

A more pronounced impairment of kidney function in PRL patients was exhibited by significantly higher neopterin serum values during the lavage period compared with the PAC group ( $103.1 \pm 29.5$  nmol/L in the PRL group vs  $39.4 \pm 9.0$  nmol/L in the PAC group;



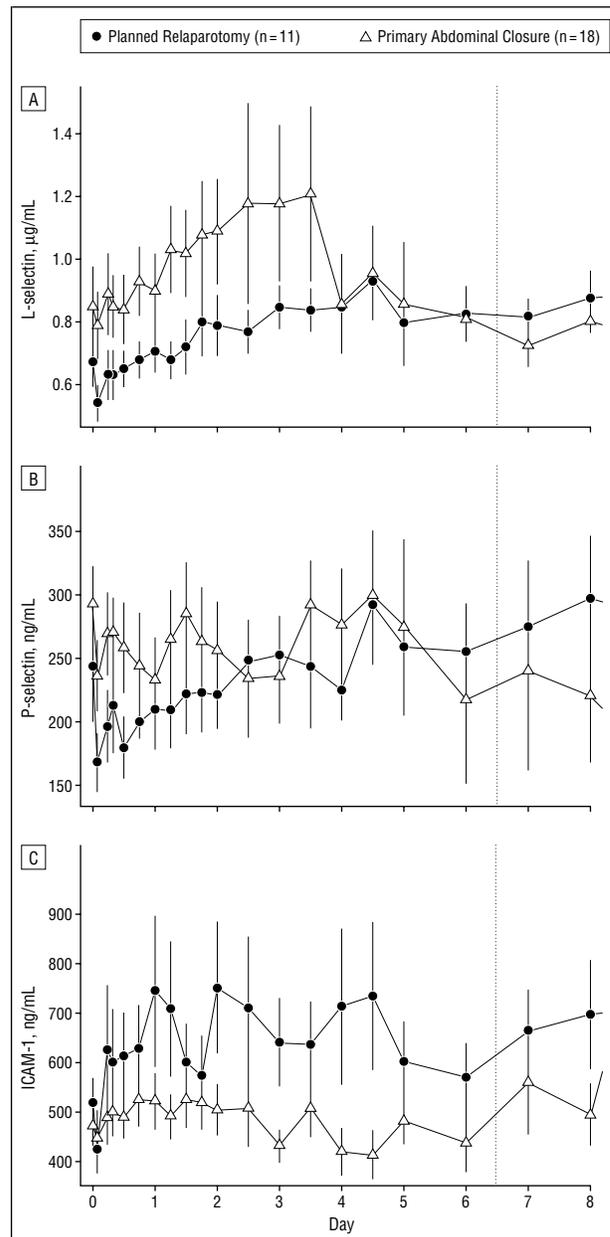
**Figure 6.** C3 complement (A) and opsonization capacity (B) in the circulation in patients with peritonitis. Error bars indicate SEM; asterisk, Wilcoxon *U* test,  $P < .05$ ; and dashed line, end of planned relaparotomy period.

$P = .04$ ). Likewise, serum creatinine levels were above the standard range after the third day only in the PRL group (Figure 8).

### COMMENT

The indication for PRL in secondary peritonitis is not yet settled with certainty.<sup>5,17,18</sup> Generally, the positive results of the studies by Penninckx et al<sup>1</sup> and Teichmann et al<sup>2</sup> stimulated European physicians to perform PRLs in patients with diffuse peritonitis.<sup>19</sup> Nevertheless, operations are major interventions in the integrity of an organism and result in disturbance of the whole body homeostasis.<sup>20-22</sup> Alterations of virtually every hormonal feedback mechanism have been described as a consequence of operative trauma associated with the release of catecholamines, glucocorticoids, growth hormones, and glucagon and the suppression of insulin secretion.<sup>11,23,24</sup> Several studies have shown that the extent of postoperative changes depends on the nature and scope of the operation. This applies as much to cortisone, noradrenaline, and angiotensin-converting enzymes as it does to glucagon and growth hormones.<sup>23,25</sup> Consequently, alterations in hormonal feedback mechanism initiate modulations of metabolic capacity,<sup>23</sup> with hyperglycemia being the most pertinent.<sup>26</sup>

However, besides the detrimental effects, scheduled additional operations allow early identification of complications<sup>1,27</sup> and reduction of bacterial counts, toxins, and

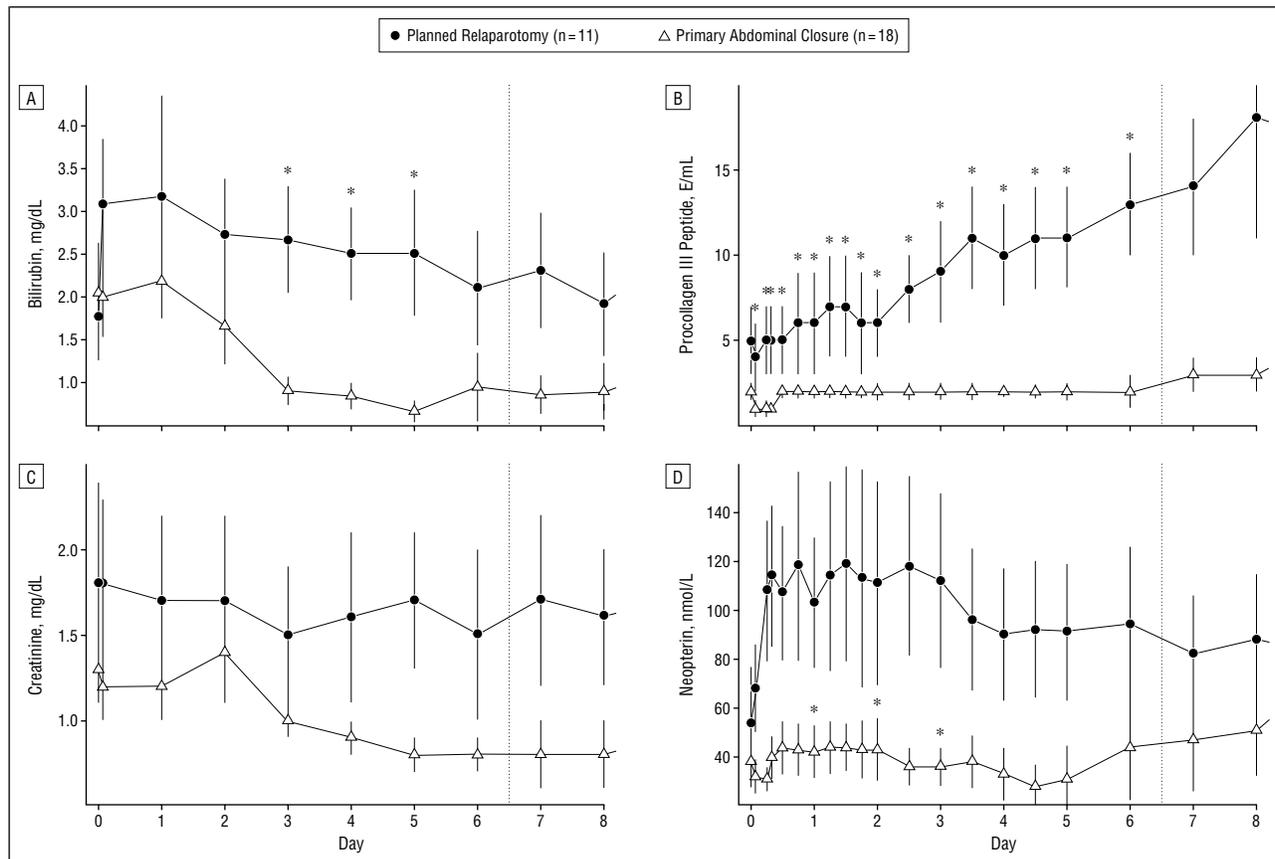


**Figure 7.** Soluble adhesion molecules (L-selectin [A], P-selectin [B], and ICAM-1 [intercellular adhesion molecule 1] [C]) in the circulation in patients with peritonitis. Error bars indicate SEM; asterisk, Wilcoxon *U* test,  $P < .05$ ; dashed line, end of planned relaparotomy period.

other sepsis mediators.<sup>2,11</sup> Yet, to our knowledge, no prospective study thus far has demonstrated a clear improvement in the postoperative phase, except a minor reduction in mortality as a result of PRL.<sup>3,4,6,28</sup> Hau et al<sup>7</sup> warned of a higher incidence of anastomosis leakage with recurrent intra-abdominal infections and septicemia occurring during additional operations. Therefore, PRL should be reserved for a narrow spectrum of indications, such as intra-abdominal hypertension or missing source control.<sup>29</sup>

### HEMOSTASIS

Operation-induced coagulation disturbances as assessed by the routine laboratory parameters, such as PTT, PT, and



**Figure 8.** Organ function parameters in the circulation in patients with peritonitis (bilirubin [A], procollagen III peptide [B], creatinine [C], and neopterin [D]). Error bars indicate SEM; asterisk, Wilcoxon *U* test,  $P < .05$ ; and dashed line, end of planned relaparotomy period. To convert bilirubin values to micromoles per liter, multiply by 17.1. To convert creatinine values to micromoles per liter, multiply by 88.4.

thrombocyte count, have been described in several publications.<sup>30-33</sup> Loss of coagulation factors may be due to proteolytic destruction,<sup>34</sup> hemorrhage, and dilution effects.<sup>35</sup> In our study, a significantly higher use of fresh frozen plasma during the PRL period may have caused PTT and PT to remain on the same pathological level as in the PAC group despite a more pronounced consumption of coagulation factors in PRL patients. Moreover, the amount of blood loss manifesting itself by red blood cell requirements was significantly higher in the PRL group, indicating further an unfavorable impact of PRL on the coagulation system. The greater bleeding tendency in the PRL group was also reflected by the thrombocyte count. Although only patients in the PRL group received thrombocyte concentrates, the thrombocyte cell count was still significantly lower than in the primary abdominal closure collective. The more pronounced activation of prothrombin and the inhibition of active thrombin by antithrombin as a strong indication of coagulation activation<sup>36-38</sup> were demonstrated by the increase of the prothrombin fragment 1 + 2 and the TAT complex during the PRL period.

#### ACUTE-PHASE PROTEINS, CYTOKINES, AND ADHESION MOLECULES

Secondary peritonitis usually triggers a generalized systemic inflammatory response. This is suggested by the release of a multitude of indicators and mediators of inflam-

mation, which were shown to correlate with the severity of the disease and/or prognosis of sepsis patients.<sup>39-52</sup> For most of the factors, our study confirmed clearly pathological plasma and serum values not only before but in particular after the primary operation. A further rise in the early postoperative phase and/or at least a delayed decline was apparent for the common acute-phase reactant C-reactive protein, the infection-related procalcitonin, and proinflammatory parameters of the cytokine system (IL-6, IL-8), especially in patients undergoing PRL treatment. Surprisingly, plasma concentrations of soluble L-selectin and P-selectin as indicators of granulocyte, thrombocyte, and endothelial cell activation were conspicuously lower in the PRL patients during the PRL phase compared with the PAC group. Since we had expected that these adhesion molecules would increase during PRL, an explanation for the opposite findings may be that in cases of severe organ failure, part of the soluble adhesion molecules is bound by activated endothelial and other inflammatory cells, thus being removed from the circulation. This assumption has been verified at least for soluble L-selectin in severely ill patients with acute respiratory distress syndrome studied by Donnelly et al.<sup>53</sup>

#### PARAMETERS OF OPSONIZATION

As previously demonstrated by Billing et al,<sup>54,55</sup> the elution of defense components by PRL treatment of perito-

nitis patients also led to a systemic drop in C3 level and a reduction in opsonization capacity, whereas the IgG concentration in the plasma remained unchanged. In agreement with these findings, pathological alterations of parameters of opsonization were continuously more pronounced in the PRL group.

### ORGAN FUNCTION PARAMETERS

A direct effect of the combination of peritonitis and operation trauma as induced by PRL could be demonstrated on various organ systems. Thus, renal function impairment, as represented by the decreased elimination of serum creatinine and neopterin,<sup>56-58</sup> became especially obvious for the macrophage metabolite neopterin during the PRL period. In addition, the increase of P-III-P and bilirubin as markers of reduced hepatic elimination<sup>59</sup> was even more noticeable, because both parameters remained significantly higher throughout PRL treatment.

Although the reduced intra-abdominal pressure in the PRL group is expected to improve oxygenation,<sup>60</sup> the PaO<sub>2</sub>/FIO<sub>2</sub> quotient of our patients was persistently worse during lavage treatment than after PAC. This finding is in line with a former study on critically ill patients, whose increase in the alveolar-arterial oxygen gradient became reversible in surviving subjects, whereas the pulmonary impairment persisted in patients with lethal outcome.<sup>61,62</sup> The worsening of pulmonary function in our PRL patients may have several causes. Most probably, additional intervention-related inflammation responses and mediator releases may have induced interstitial edema formation, resulting in deterioration of oxygenation,<sup>24</sup> which is reflected in the protracted duration of respiratory supports and hence in the longer ICU hospitalization of PRL patients.

The pathophysiological changes during and after surgical interventions are known to affect not only organ systems, such as liver, kidney, and lungs, but also the cardiocirculatory system. The complex interrelations among cardiac output, vascular resistance, oxygen transport, and oxygen consumption have been intensively investigated in several studies.<sup>24,61,63,64</sup> Although not shown in detail herein, cardiocirculatory changes in our patient collectives are included in the sequential measurements of the APACHE II, MOF, and SOFA scores<sup>13-15</sup> and may have contributed additionally to the significantly elevated levels of the MOF and SOFA scores in PRL patients compared with PAC subjects. Thus, the higher severity of organ dysfunctions resulted eventually in a higher mortality in the PRL group.

In conclusion, in our pilot study on PRL effects on secondary peritonitis, PRL increased the need for erythrocytes, thrombocytes, and fresh frozen plasma. The IL-8 levels increased significantly, and all other cytokines showed a tendency to increase, suggesting an enhancement of the inflammatory mediator response with a longer duration of mechanical ventilation and ICU stay compared with PAC patients. Therefore, PRL may act as an additional inflammatory stimulus ("second hit")<sup>65,66</sup> in an already weakened organism prone to MOF. Thus, above all the progression of acute respiratory distress syn-

drome may be a consequence of PRL. Our extended biochemical and clinical data support recent suggestions that indications for PRL should be restricted to unsecured or lacking focal source control and signs of intra-abdominal hypertension.<sup>7,29</sup>

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### REFERENCES

1. Penninckx FM, Kerremans RP, Lauwers PM. Planned relaparotomies in the surgical treatment of severe generalized peritonitis from intestinal origin. *World J Surg.* 1983;7:762-766.
2. Teichmann W, Wittmann DH, Andreone PA. Scheduled reoperations (etappenlavage) for diffuse peritonitis. *Arch Surg.* 1986;121:147-152.
3. Andrus C, Doering M, Herrmann VM, Kaminski DL. Planned reoperation for generalized intraabdominal infection. *Am J Surg.* 1986;152:682-686.
4. Schein M, Saadia R, Freinkel Z, Decker GA. Aggressive treatment of severe diffuse peritonitis: a prospective study. *Br J Surg.* 1988;72:173-176.
5. Schein M. Planned reoperations and open management in critical intra-abdominal infections: prospective experience in 52 cases. *World J Surg.* 1991;15:537-545.
6. Koperna T, Schulz F. Relaparotomy in peritonitis: prognosis and treatment of patients with persisting intraabdominal infection. *World J Surg.* 2000;24:32-37.
7. Hau T, Ohmann C, Wolmershauser A, Wacha H, Yang Q, for the Peritonitis Study Group of the Surgical Infection Society-Europe. Planned relaparotomy vs relaparotomy on demand in the treatment of intra-abdominal infections. *Arch Surg.* 1995;130:1193-1196.
8. Teichmann W, Herbig B. Therapy principles in diffuse peritonitis [in German]. *Chirurg.* 2000;71:120-128.
9. Pichlmayr R, Weimann A, Klempnauer J. Continuous irrigation or staged lavage in peritonitis? [in German]. *Chirurg.* 1992;63:162-168.
10. Sauter T, Göttinger P, Redl-Wenzl EM, et al. Does reoperation for abdominal sepsis enhance the inflammatory host response? *Arch Surg.* 1997;132:250-255.
11. Holzheimer RG, Schein M, Wittmann DH. Inflammatory response in peritoneal exudate and plasma of patients undergoing planned relaparotomy for severe secondary peritonitis. *Arch Surg.* 1995;130:1314-1320.
12. Lindner MM, Wacha A, Feldmann U, Wesch G, Steifensand RA, Gundlach E. The Mannheim Peritonitis Index: an instrument for intraoperative prognosis of peritonitis [in German]. *Chirurg.* 1987;58:84-92.
13. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985;13:818-829.
14. Goris RJ, te Boekhorst TP, Nuytinck JK, Gimbriere JS. Multiple-organ failure: generalized autodestructive inflammation? *Arch Surg.* 1985;120:1109-1115.
15. Vincent JL, Moreno R, Takala J, et al, on behalf of the Working Group on Sepsis-related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med.* 1996;22:707-710.
16. Billing A, Kortmann H, Fröhlich D, Jochum M. Breakdown of C3 complement and IgG in peritonitis exudate: pathophysiological aspects and therapeutic approach. *Prog Clin Biol Res.* 1989;308:527-533.
17. Farthmann EH, Schöffel U. Principles and limitations of operative management of intraabdominal infections. *World J Surg.* 1990;14:210-217.
18. Wittmann DH, Schein M, Condon RE. Management of secondary peritonitis. *Ann Surg.* 1996;224:10-18.
19. Koperna T, Schulz F. Prognosis and treatment of peritonitis: do we need new scoring systems? *Arch Surg.* 1996;131:180-186.
20. Holmdahl L, Eriksson E, Al-Jabreen M, Risberg B. Fibrinolysis in human peritoneum during operation. *Surgery.* 1996;119:701-705.
21. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth.* 1997;78:606-617.

22. Pape HC, Stalp M, Griensven M, Weinberg A, Dahlweit M, Tscherne H. Optimal timing for secondary surgery in polytrauma patients: an evaluation of 4314 serious injury cases [in German]. *Chirurg*. 1999;70:1287-1293.
23. Anand KJS. The stress response to surgical trauma: from physiological basis to therapeutic implications. *Prog Food Nutr Sci*. 1986;10:67-132.
24. Kehlet H, Nielson HJ. Impact of laparoscopic surgery on stress responses, immunofunction, and risk of infectious complications. *New Horizons*. 1998;6:80-88.
25. Chernow B, Alexander HR, Smalridge RC, et al. Hormonal responses to graded surgical stress. *Arch Intern Med*. 1987;147:1273-1278.
26. Fauth U, Heinrichs W, Puente-Gonzalez I, Halmagyi M. Maximal turnover rates of glycolysis enzymes and of the citrate cycle of separated granulocytes in the postoperative period [in German]. *Infusionstherapie*. 1990;17:178-183.
27. Bosscha K, Hulstaert PF, Visser MR, van Vroonhoven TJ, van der Werken. Open management of the abdomen and planned reoperation in severe bacterial peritonitis. *Eur J Surg*. 2000;166:44-49.
28. Leiboff AR, Soroff HS. The treatment of generalized peritonitis by closed postoperative peritoneal lavage: a critical review of the literature. *Arch Surg*. 1987;122:1005-1010.
29. Seiler CA, Brügger L, Forsmann U, Baer HU, Büchler MW. Conservative surgical treatment of diffuse peritonitis. *Surgery*. 2000;127:178-184.
30. Jorgenson KA, Stoffersen E, Sorensen PJ, Ingeberg S, Hüttel M, Ahlbom G. Alterations in plasma antithrombin III following total hip replacement and elective cholecystectomy. *Scand J Haematol*. 1980;24:101-104.
31. Bueller HR, ten Cate JW. Acquired antithrombin III deficiency: laboratory diagnosis, incidence, clinical implications, and treatment with antithrombin III concentrate. *Am J Med*. 1989;87:44-48.
32. Murphy WG, Davies MJ, Eduardo A. The haemostatic response to surgery and trauma. *Br J Anaesth*. 1993;70:205-213.
33. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth*. 2000;85:109-117.
34. Jochum M, Gippner-Steppert C, Machleidt W, Fritz H. The role of phagocyte proteinases and proteinase inhibitors in multiple organ failure. *Am J Respir Crit Care Med*. 1994;150:123-130.
35. Blauhut B, Lundsgaard-Hansen P. Hemostatic disorders in anesthesiology and surgical intensive care. *Anaesthesiol Reanim*. 1990;15:67-80.
36. Asakura H, Shiratori Y, Jokaji H, et al. Changes in plasma levels of prothrombin fragment F 1 + 2 in cases of disseminated intravascular coagulation. *Acta Haematol*. 1993;89:22-25.
37. Okamoto K, Takaki A, Takeda S, Katoh H, Onsato K. Coagulopathy in disseminated intravascular coagulation due to abdominal sepsis: determination of prothrombin fragment 1 + 2 and other markers. *Haemostasis*. 1992;22:17-24.
38. Okajima K, Uchiba M, Murakami K, Okabe H, Takatsuki K. Determination of plasma soluble fibrin using a new ELISA method in patients with disseminated intravascular coagulation. *Am J Hematol*. 1996;51:186-191.
39. Damas P, Ledoux D, Nys M, et al. Cytokine serum level during severe sepsis in human IL-6 as a marker of severity. *Ann Surg*. 1992;215:356-362.
40. Gardlund B, Sjölin J, Nilsson A, Roll M, Wickerts CJ, Wretling B. Plasma levels of cytokines in primary septic shock in humans: correlation with disease severity. *J Infect Dis*. 1995;172:296-301.
41. Pruitt JH, Copeland EM III, Moldawer LL. Interleukin-1 and interleukin-1 antagonism in sepsis, systemic inflammatory response syndrome, and septic shock. *Shock*. 1995;3:235-251.
42. Miller EJ, Cohen AB, Matthey MA. Increased interleukin-8 concentration in the pulmonary edema fluid of patients with acute respiratory distress syndrome from sepsis. *Crit Care Med*. 1996;24:1448-1454.
43. Biffi WL, Moore EE, Moore FA, Barnett CC Jr, Carl VS, Peterson VW. Interleukin-6 delays neutrophil apoptosis. *Arch Surg*. 1996;131:24-30.
44. Fröhlich D, Eiber RM, Jochum M, Billing A. Perioperative pattern of peritoneal interleukin-8, tumor necrosis factor- $\alpha$ , and granulocyte elastase release in human secondary peritonitis. *Cytokine*. 1997;9:288-292.
45. Hamano K, Gohra H, Noda H, et al. Increased serum interleukin-8 correlation with poor prognosis in patients with postoperative multiple organ failure. *World J Surg*. 1998;22:1077-1081.
46. Inthorn D, Hoffmann JN, Hartl WH, Mühlbayer D, Jochum M. Effect of antithrombin III supplementation on inflammatory response in patients with severe sepsis. *Shock*. 1998;10:90-96.
47. Wakefield CH, Barclay GR, Fearon KC, et al, for the Scottish Sepsis Intervention Group. Proinflammatory mediator activity, endogenous antagonists and the systemic inflammatory response in intra-abdominal sepsis. *Br J Surg*. 1998;85:818-825.
48. Scheingraber S, Scharbert G, Böhme J, Bauernfeind F, Dralle H. Cytokine kinetics during peritoneal lavage [abstract]. *Shock*. 1999;12(suppl):61.
49. Herrmann W, Ecker D, Quast S, Klieden M, Rose S, Marzi I. Comparison of procalcitonin, sCD14 and interleukin-6 values in septic patients. *Clin Chem Lab Med*. 2000;38:41-46.
50. Serafini FM, Rosemurgy AS. Adhesion molecules: clinical implications. *Surgery*. 2000;127:481-483.
51. Selberg O, Hecker H, Martin M, et al. Discrimination of sepsis and systemic inflammatory response syndrome by determination of circulating plasma concentrations of procalcitonin, protein complement 3a, and interleukin-6. *Crit Care Med*. 2000;28:2791-2798.
52. Brunkhorst FM, Wegscheider K, Forycki ZF, et al. Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. *Intensive Care Med*. 2000;26:148-152.
53. Donnelly CS, Haslett C, Dransfield I, et al. Role of selectins in development of adult respiratory distress syndrome. *Lancet*. 1994;4:215-219.
54. Billing A, Fröhlich D, Mialkowskyj O, Stokstad P, Schildberg FW. Treatment of peritonitis with staged lavage: prognostic criteria and course of treatment. *Langenbecks Arch Surg*. 1992;377:305-313.
55. Billing A, Fröhlich D, Konecny G, et al. Local serum application: restoration of sufficient host defense in human peritonitis. *Eur J Clin Invest*. 1994;24:28-35.
56. Strohmaier W, Redl H, Schlag G, Inthorn D. D-erythro-neopterin plasma levels in intensive care patients with and without septic complications. *Crit Care Med*. 1987;15:757-760.
57. Waydhas C, Nast-Kolb D, Jochum M, et al. Inflammatory mediators, infection, sepsis, and multiple organ failure after severe trauma. *Arch Surg*. 1992;127:460-467.
58. Fuchs D, Stahl-Hennig C, Gruber A, Murr C, Hunsmann G, Wachter H. Neopterin: its clinical use in urinalysis. *Kidney Int*. 1994;46:8-11.
59. Waydhas C, Nast-Kolb D, Trupka A, et al. Increased serum concentrations of procollagen type III peptide in severely injured patients: an indicator of fibrosing activity? *Crit Care Med*. 1993;21:240-247.
60. Sugrue M, Jones F, Deane SA, Bishop G, Bauman A, Hillman K. Intra-abdominal hypertension is an independent cause of postoperative renal impairment. *Arch Surg*. 1999;134:1082-1085.
61. Hayes MA, Timmins AC, Yau EH, Palazzo M, Watson D, Hinds CJ. Oxygen transport patterns in patients with sepsis syndrome of septic shock: influence of treatment and relationship to outcome. *Crit Care Med*. 1997;25:926-936.
62. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. *Crit Care Med*. 1998;26:1793-1800.
63. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA*. 1994;270:2699-2707.
64. Goor van H. Surgical treatment of severe intra-abdominal infection. *Hepatogastroenterology*. 1997;44:975-981.
65. Wang SC, Klein RD, Wahl WL, et al. Tissue coexpression of LBP and CD14 mRNA in a mouse model of sepsis. *J Surg Res*. 1998;76:67-73.
66. Ogura H, Tanaka H, Kohl T, et al. Priming, second-hit priming, and apoptosis in leukocytes from trauma patients. *J Trauma*. 1999;46:774-783.