Impact of Blood Transfusions on Inflammatory Mediator Release in Patients Undergoing Cardiac Surgery*

Erik Fransen, PhD; Jos Maessen, MD, PhD; Mieke Dentener, PhD; Nicole Senden, PhD; and Wim Buurman, PhD

Study objectives: This study was conducted to investigate whether intraoperative blood transfusions affect the release of proinflammatory mediators in patients undergoing cardiac surgery. Therefore, we measured plasma levels of bactericidal permeability increasing protein (BPI) as a marker of neutrophil activation, interleukin-6 (IL-6), lipopolysaccharide binding protein (LBP), and C-reactive protein (CRP). In addition, these mediators, except CRP, were also measured in packed red cell units (PCs) administered to these patients.

Design: Prospective study.

Setting: Cardiopulmonary surgery department in a university hospital.

Patients: One hundred fourteen consecutive patients undergoing cardiac surgery.

Interventions: Blood samples were taken at induction of anesthesia, at the start of aortic cross-clamping, at aortic unclamping, and at 0.5, 4, 8, and 18 h thereafter.

Results: Thirty-six patients received PC intraoperatively. BPI levels in patients who received transfusions were significantly higher at 0.5 and 4 h after aortic unclamping than in patients without transfusions (p < 0.05), and increased with the number of PC administered. IL-6 levels at 0.5, 4, and 18 h after aortic unclamping were also significantly higher in patients who received transfusions (p < 0.01). BPI was found in all units of packed red cells tested at concentrations up to 15 times preoperative plasma levels in patients. However, PC IL-6 could be detected in none of the samples. Plasma levels of LBP and CRP were similar in both patient groups. LBP was found in very low concentrations in all PC. Patients who received intraoperative transfusions had a worse postoperative performance.

Conclusions: Intraoperative PC transfusions do contribute to the inflammatory response after cardiac surgery both by enhancing part of the response and by directly changing plasma concentrations of inflammatory mediators. Furthermore, these data show that intraoperative PC transfusion is associated with a worse postoperative performance.

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Key words: blood transfusions; cardiac surgery; inflammatory mediators

Abbreviations: BPI = bactericidal permeability increasing protein; CPB = cardiopulmonary bypass; CRP = C-reactive protein; ELISA = enzyme-linked immunosorbent assay; IL-6 = interleukin-6; LBP = lipopolysaccharide binding protein; PC = packed red cell unit; PMN = polymorphonuclear leukocytes

In previous studies,1,2 we showed that the extent of the systemic inflammatory response to cardiac surgery is not primarily determined by the cardiopulmonary bypass (CPB) procedure. Other factors, such as intrinsic patient factors and intraoperative trauma, also play a role in determining the extent of the inflammatory response. In the present study, we present data on the impact of the administration of routinely used allogeneic blood transfusions during cardiac surgery on plasma levels of circulating inflammatory mediators.

The administration of allogeneic blood transfusions is a common procedure in cardiac surgery. However, along with its beneficial effects, allogeneic blood transfusions have been reported to suppress
the immune system, thereby contributing to patient morbidity during recovery.\textsuperscript{3,4} Previous studies\textsuperscript{5} showed that the plasma supernatant of blood transfusion products contain bioactive substances that cause febrile reactions. Therefore, we examined whether administration of packed red cells to patients undergoing cardiac surgery, during the course of the operation, affects the release of inflammatory mediators into plasma in these patients. In addition, we examined the correlation of intraoperative packed red cell transfusion and patient morbidity during postoperative recovery.

For this study, we measured bacteridal permeability increasing protein (BPI) levels as a marker of activation of polymorphonuclear leukocytes (PMN), interleukin 6 (IL-6), and the acute-phase proteins lipopolysaccharide binding protein (LBP) and C-reactive protein (CRP) in 114 patients undergoing cardiac surgery, of whom 36 received at least one allogeneic packed red cell unit (PC) during surgery. In addition, we checked for the presence of BPI, IL-6, and LBP in packed red cells that were administered to these patients. Furthermore, we documented variables of postoperative performance.

\textbf{Materials and Methods}

\textbf{Patients}

A total of 114 consecutive adult patients undergoing coronary artery bypass grafting and/or valve surgery with CPB were enrolled. Age boundaries were set at 30 and 80 years old. Patients with current infection, hematologic or endocrinologic disease, or a history of organ transplantation or blood transfusions were excluded. Retrospectively, this cohort was analyzed and divided in two groups, those who received allogeneic packed red cells intraoperatively, and those who did not. All subjects gave informed consent for the study, which was approved by the local ethical and research council.

\textbf{Intraoperative Patient Management}

Standard anesthetic (lorazepam, fentanyl citrate, sufentanil citrate, alfentanil hydrochloride, midazolam hydrochloride, pancuronium bromide) and monitoring techniques (ECG, arterial pressure monitoring, urinary output, rectal and skin temperature monitoring) were used in all patients. Cefuroxime was used for antibiotic prophylaxis, the first dose was administered before sternotomy.

Before connection to the non-heparin-coated extracorporeal circuit for CPB, porcine heparin (300 IU/kg [Heparin Leo; Mijdrecht, The Netherlands]) was administered to achieve an activated coagulation time of 480 s. Immediately after sampling, the blood was centrifuged at 3,500 rpm for 20 min, and plasma samples were stored at \(-70\)°C until measurements were performed.

\textbf{Measurements}

Plasma levels of BPI, IL-6, and LBP were measured using sandwich enzyme-linked immunosorbent assays (ELISA), which have been described elsewhere.\textsuperscript{7-9} In short, 96-well plates (Immu-no-Maxisorp; Nunc; Roskilde, Denmark) were coated with the appropriate antibodies. For BPI, IL-6, and LBP measurements, human BPI-specific monoclonal antibody (MoAb) 4E3, murine MoAb 5E1, and polyclonal anti-human LBP IgG, respectively, were used as coatings. Free sites were blocked with 1% bovine serum albumin in phosphate-buffered saline solution. Samples and standard dilution series were added for 2 h. Human recombinant BPI (kindly provided by M. Marra; Incyte; Palo Alto, CA), human recombinant IL-6 (a kind gift from Prof. W. Sebald; Psychologisch-Chemisches Institut der Universität Würzburg; Germany), and human recombinant LBP were used for standard titration curves. Human recombinant LBP was administered to achieve an activated coagulation time of 480 s.
obtained from supernatant of Chinese hamster ovary cells transfected with cDNA of human LBP (kindly provided by Dr. P. Tobias; Scripps Research Institute; La Jolla, CA). In case of the BPI and LBP ELISA, washing and dilution buffers contained 80 or 40 mM magnesium chloride, respectively, to prevent disturbance by lipopolysaccharide. Biotinylated polyclonal rabbit anti-human BPI IgG, biotinylated polyclonal rabbit anti-human IL-6 antiserum, and polyclonal rabbit anti-human LBP IgG were used as detection antibodies. The detection limits for the ELISAs were 200 pg/mL for the BPI-assay, 10 pg/mL for IL-6, and 500 pg/mL for LBP. Biotinylated antibodies were detected with peroxidase-conjugated streptavidin (Zymed; San Francisco, CA). Finally, 3,3',5,5'-tetramethylbenzidine (Kirkegaard & Perry Laboratories; Gaithersburg, MD) was used as a substrate. Photospectrometry (450 nm) was performed using a micro-ELISA autoreader. All plasma samples were analyzed in the same run.

CRP concentrations were measured using a turbidimetric method. A CRP reagent (Beckman test kit number 445855), in conjunction with the Synchron CX Systems CX CRP Calibrator Set (Beckman, number 445915; Beckman Instruments; Brea, CA), was used for the quantitative determination of CRP in serum. CRP levels were determined on the day before surgery, and on days 1, 2, 4, and 6 after surgery.

Clinical Variables

The following variables were recorded: type of surgery, time until weaning from ventilation, postoperative stay in the ICU, diuresis during the first 24 postoperative hours, total mediastinal fluid drainage, length of postoperative hospitalization, incidence of postoperative infection during hospitalization, and mortality. Centers for Disease Control and Prevention definitions for nosocomial infections were used for diagnosing postoperative infections.10 All infections were diagnosed during hospitalization.

Data Analysis

Repeated-measures analysis of variance was used to compare changes in time between both patient groups. The Mann Whitney U test was added to isolate significant differences between both experimental groups at a single, predetermined time. A Wilcoxon matched-pairs signed-ranks test was used for comparisons of values from one variable between two times. Incidence of variables was analyzed by a \( \chi^2 \) test. Independent predictive value of variables was assessed by multiple regression analysis. Differences were considered significant at \( p < 0.05 \). All data are presented as mean \( \pm \) SEM.

RESULTS

Clinical Characteristics

The intraoperative characteristics of both patient groups are shown in Table 1. From the total group of 114 patients, 36 patients received packed red blood cells intraoperatively (17 received 1 U, 8 received 2 U, 10 received 3 U, and 1 patient received 4 U of packed RBCs). The significant differences between the patient groups for age, height, weight, and sex will be discussed later.

Inflammatory Mediators

To study neutrophil activation, BPI plasma levels were measured. Baseline levels of BPI were similar in both groups and increased from the start of aortic clamping until the first postoperative day (\( p < 0.05 \) at all times; Fig 1, top left, A). Peak levels of 8 times baseline levels were reached at the end of aortic clamping in control patients, and 17 times baseline levels in patients who received transfusions. At 0.5 and 4 h after the start of reperfusion, BPI levels were significantly higher in patients who received transfusions (\( p < 0.01 \)). To study the acute-phase response, IL-6, LBP, and CRP were measured. Baseline levels of IL-6 were similar in both groups, \( 0.07 \pm 0.01 \) vs \( 0.09 \pm 0.03 \) ng/mL (Fig 1, top right, B). In the control group, IL-6 levels decreased during CPB, subsequently increased and peaked at 8 h after reperfusion (6 times above baseline levels), and remained elevated until the first postoperative day. In the transfusion group, IL-6 levels increased from the start of reperfusion and peaked at 4 h after reperfusion (9 times higher than baseline levels). The IL-6 response was significantly different between both groups by analysis of variance for repeated measures (\( p < 0.05 \)), ie, IL-6 levels reached maximum plasma levels earlier in patients who received transfusions. At 0.5, 4, and 18 h after reperfusion, IL-6 levels were significantly higher in patients who received transfusions (\( p < 0.05 \)).

Mean preoperative plasma levels of the acute-phase protein LBP were \( 32.4 \pm 4 \) and \( 40.0 \pm 5 \) \( \mu \)g/mL in the control group and transfusion group, respectively (Fig 1, bottom left, C). In both groups, LBP plasma levels decreased during surgery (until 0.5 h after reperfusion; \( p < 0.01 \)), and gradually increased between 0.5 and 18 h after reperfusion (\( p < 0.01 \)).

Mean preoperative plasma levels of CRP were \( 11.5 \pm 3 \) and \( 12.1 \pm 4 \) mg/L in the control group and

| Table 1—Intraoperative Characteristics of the Two Patient Groups* |
|----------------|----------------|----------------|
| Characteristics | Controls \( n = 78 \) | PC Group \( n = 36 \) | \( p \) Value |
| Age, yr | 61 \( \pm \) 1 | 67 \( \pm \) 1 | \( p < 0.05 \) |
| Height, cm | 172 \( \pm \) 1 (150–190) | 165 \( \pm \) 1 (150–185) | \( p < 0.05 \) |
| Weight, kg | 80 \( \pm \) 1 (52–121) | 72 \( \pm \) 2 (50–99) | \( p < 0.05 \) |
| Sex | | | |
| Male | 67 | 13 | \( p < 0.05 \) |
| Female | 11 | 23 | \( p < 0.05 \) |
| Type of surgery | | | |
| CABG | 69 (85.5%) | 27 (75%) | NS |
| Valve | 6 (7.7%) | 6 (16.7%) | NS |
| CABG + valve | 3 (3.8%) | 3 (8.3%) | NS |
| CPB duration, min | 90 \( \pm \) 4 (36–205) | 102 \( \pm \) 6 (53–193) | NS |
| ACC duration, min | 59 \( \pm \) 3 (21–146) | 66 \( \pm \) 5 (8–142) | NS |

*Data are presented as mean \( \pm \) SEM. ACC = aortic cross-clamping; CABG = coronary artery bypass graft; NS = not significant.
transfusion group, respectively (Fig 1, bottom right, D). On the first postoperative day, CRP levels were significantly increased in both groups, to 86.9 ± 3 mg/L in the control group and 82.6 ± 7 mg/L in the transfusion group. CRP levels reached their highest mean plasma levels on day 2 after surgery and gradually decreased thereafter. All postoperative CRP levels were significantly elevated from baseline levels (p < 0.01). Both LBP and CRP levels did not significantly differ between both patient groups at any time.

**Clinical Data**

Preoperative hematocrit values and hemoglobin levels were significantly lower in the transfusion group than in the control group, 32 ± 6% vs 38 ± 4% (p < 0.001), and 7.2 ± 0.1 vs 8.5 ± 0.1 mmol/L (p < 0.001), respectively. Hematocrit values and hemoglobin levels decreased postoperatively without differences between the patient groups. On the first postoperative day, hematocrit values and hemoglobin levels were 29 ± 4% and 6.2 ± 0.1 mmol/L in the transfusion group, and 30 ± 3% and 6.3 ± 0.1 mmol/L in the control group. Both hematocrit values and hemoglobin levels did not significantly differ between both patient groups at this time.

Time until weaning from ventilation was significantly longer in patients who received transfusions than in control patients: 42 ± 12 vs 22 ± 2 h (Table 2). Furthermore, postoperative length of stay on the cardiac surgical ICU until transportation to the ward was significantly longer in patients who received transfusions (Table 2). Postoperative mediastinal bleeding and postoperative diuresis during the first 24 postoperative hours did not significantly differ

**Table 2—Variables of Postoperative Performance of the Two Patient Groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n = 78)</th>
<th>PC Group (n = 36)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time until extubation, h</td>
<td>22 ± 2</td>
<td>42 ± 12</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Time until transport to the ward, h</td>
<td>45 ± 6</td>
<td>89 ± 21</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Diuresis until 24 h postoperatively, mL</td>
<td>2.362 ± 108</td>
<td>2.144 ± 159</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative mediastinal bleeding, mL</td>
<td>1.358 ± 92</td>
<td>1.272 ± 112</td>
<td>NS</td>
</tr>
<tr>
<td>Incidence of postoperative infections, %</td>
<td>10.3</td>
<td>19.4</td>
<td>0.17</td>
</tr>
<tr>
<td>Postoperative hospitalization, days</td>
<td>7.2 ± 0.4</td>
<td>10.6 ± 1.6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Data are presented as means ± SEM. See footnote of Table 1 for abbreviations.
between both groups (Table 2). The incidence of postoperative infections in control patients and in patients who received transfusions was not significantly different (odds ratio = 2.12; 95% confidence interval, 0.70 to 6.36). However, the duration of postoperative hospitalization was significantly longer in patients who received transfusions than in control patients (Table 2).

**Inflammatory Mediators in the PCs**

To determine whether substances in the packed red cells affect inflammatory mediator levels in the recipient, BPI, IL-6, and LBP were measured in the PCs. The allogeneic PCs contained an average of 21.55 ± 4.9 ng/mL BPI (range, 4.56 to 50 ng/mL), and 600.5 ± 66 ng/mL LBP (range, 271 to 900 ng/mL). In contrast, no IL-6 could be detected in any of the PCs. BPI levels, but not LBP levels, progressively increased with storage time. In PCs with an age of 2 days, BPI levels averaged approximately 10 ng/mL, whereas in PCs of 31 days of age, BPI levels were approximately 50 ng/mL, suggesting disintegration of PMNs present in the packed cells.

**Analysis of Risk Factors for Red Cell Transfusion and Postoperative Morbidity**

Using retrospective group stratification, we found significant differences between control patients and patients who received transfusions with respect to age, height, weight, the distribution of sex (Table 1), and preoperative hematocrit and hemoglobin levels. A stepwise multiple regression analysis including these variables as independent variables and the administration of packed red cells during surgery as the dependent variable revealed, as expected, that preoperative hematocrit and hemoglobin levels are key determining factors in intraoperative packed RBC transfusion requirements (p < 0.001 and p = 0.023 for hematocrit and hemoglobin, respectively). Furthermore, entering age, height, weight, sex, and the intraoperative administration of packed red cells as independent variables and postoperative BPI or IL-6 levels as the dependent variable showed that the intraoperative administration of packed red cells during surgery was the most important predictor of BPI levels at aortic unclamping (p = 0.009) and 0.5 h thereafter (p = 0.002), and IL-6 levels at 0.5 (p = 0.025) and 4 h after aortic unclamping (p = 0.002). In addition, entering age, sex, and the intraoperative administration of packed red cells as independent variables and time until weaning from ventilation or postoperative stay in the ICU as the dependent variable revealed that, in both cases, the intraoperative administration of packed red cells was the most important independent variable predicting time until weaning from ventilation (p = 0.022) and postoperative stay in the ICU (p = 0.011). Therefore, despite the differences in some preoperative variables, the intraoperative administration of packed red cells during cardiac surgery is found to be significantly associated with the release of inflammatory mediators BPI and IL-6, and to coincide with impaired postoperative performance.

**Discussion**

This study provides evidence that the well-known inflammatory response to cardiac surgery, which historically has been attributed to the CPB procedure, is strongly affected by the administration of packed red cells during surgery.

In the present study, we measured BPI in plasma from patients as well as in PCs to evaluate whether cells that originate from transfusion units affect the presence of inflammatory mediators found in the recipient. BPI is a human neutrophil granule protein that has been shown to bind to lipopolysaccharide and both exerts bactericidal effects on Gram-negative bacteria and neutralizes the activities of lipopolysaccharide. In plasma, BPI is released after activation of PMNs and therefore can be used as a marker of PMN activation. In the PCs, large amounts of BPI may be released from the azurophilic granules because of PMN activation by the plastic infusion bag or PMN disintegration as a result of cold storage (4°C).11

**Transfusions and PMN Activation**

In our study, we showed a perioperative increase in BPI plasma levels, which was identical to levels that we found in previous studies,1,12 with higher levels at 0.5 and 4 h after aortic unclamping in patients who received transfusions (p < 0.05). In addition, BPI was present in all packed red cells with higher levels in units that had been stored longer. These data suggest that part of the higher BPI levels at 0.5 and 4 h after aortic unclamping in the patients who intraoperatively received transfusions may originate from the transfusion units. Indeed, calculations revealed that in patients receiving 2 U of packed red cells, approximately 15% of the total amount of BPI in plasma at 0.5 h after aortic unclamping can originate from the transfusion products (based on an estimated plasma volume of 4,500 mL). Alternatively, the BPI increase can be explained by either donor or recipient leukocytes becoming activated on transfusion, and at this time releasing their BPI from the azurophilic granules.

Several studies have shown that leukocytes present in allogeneic cellular blood components are associ-
ated with adverse effects in the recipient.\textsuperscript{3,13} The proposed immunosuppressive effects of donor leukocytes might be beneficial for some patients, \textit{eg}, for the maintenance of kidney allografts.\textsuperscript{13} In patients undergoing cardiac surgery, however, these effects may be undesirable inasmuch as these patients are already immunosuppressed by the surgical trauma. Although it is generally assumed that these effects are caused by the interaction of anti-leukocyte alloantibodies in the recipient’s plasma and WBCs in the transfusion product, Heddle et al\textsuperscript{5} recently reported that unidentified bioactive substances in the plasma supernatant produced or released by platelet products mediate reactions on transfusion.\textsuperscript{5} Our present data are in support of this view inasmuch as they confirm the presence of large amounts of BPI in packed red cells. The transfusion of BPI by giving packed red cells to a patient actually leads to increased circulating plasma levels of BPI. It cannot be deduced from our present data that higher BPI levels cause an increased postoperative morbidity.

\textbf{Transfusions and Acute-Phase Response}

In agreement with previous studies,\textsuperscript{1,14} increased plasma IL-6 levels were observed in all patients in the present study. Neutrophil- and mononuclear phagocyte-derived IL-6 is released in response to a variety of stimuli, including infection, major surgery, and thermal injury.\textsuperscript{15} IL-6 is a pleiotropic cytokine that stimulates the adhesive interaction between neutrophils and cardiac myocytes and induces the acute-phase response, and therefore it is a sensitive marker of the inflammatory response. In this study, the enhancement of IL-6 levels in control patients was significantly delayed and also lower compared with those of patients who received transfusions, although the pattern of IL-6 release was similar in both patient groups. Unlike BPI, we did not detect IL-6 in PCs, which is in agreement with findings by others.\textsuperscript{16} Interestingly, IL-6 was found by several authors in stored platelet concentrates.\textsuperscript{5,17–19} Heddle et al\textsuperscript{5} found low concentrations of IL-6, even when the concentrate was filtered before storage to remove contaminating leukocytes. In addition, they showed that IL-6 levels in the platelet concentrates progressively increased during storage and were positively correlated with the leukocyte count in the platelet product. Importantly, in their study, the platelet concentrates were stored at 22°C (vs 4°C for the packed red cells in our study), which may have affected the production and release of IL-6 in these concentrates. Although others reported that the production of proinflammatory cytokines is one of the immune functions that is depressed by allogeneic blood transfusions,\textsuperscript{20} the findings of the present study suggest that the significantly higher IL-6 plasma levels in the patients who received transfusions result from an increased IL-6 release by the recipient. Whether substances in stored blood induce this increased IL-6 release has yet to be established.

Plasma levels of CRP and LBP, two acute-phase proteins, were similar in both patient groups. CRP is the prototypical acute-phase reactant and can activate the classic pathway of complement.\textsuperscript{21} Our data support the acute-phase nature of the LBP response as well as the CRP response. Because LBP is produced by hepatocytes and was found in all PCs, the LBP in these units probably originates from the donor and is not produced or released during cold storage. This finding is supported by the fact that, unlike BPI levels, LBP levels did not increase with the length of storage. LBP levels in the PCs were low compared with LBP plasma levels and presumably did not substantially affect plasma levels (Fig 1, \textit{bottom left}, C).

Interestingly, the rise of LBP and CRP in the systemic circulation was identical in both study groups, despite the fact that we found significant differences in plasma cytokine levels (Fig 1, \textit{bottom, C and D}). Thus, the present data suggest that, in patients undergoing cardiac surgery, the amount of circulating IL-6 in the systemic circulation does not necessarily reflect the amount of acute-phase proteins produced.\textsuperscript{21,22}

\textbf{Patient Morbidity}

In patients undergoing cardiac surgery, the surgical trauma induces a noninfectious systemic inflammatory response, which is considered to play a role in the development of postoperative complications.\textsuperscript{23} Thus, in patients receiving allogeneic packed red cells, bioactive substances might serve as a second inflammatory insult, which amplifies the initial inflammatory response. This results in a further imbalance between proinflammatory and counterregulatory influences, which may lead to damage of otherwise healthy cells and organs, and thus leads to an impaired postoperative recovery. Our data support the findings by others showing that patients who received packed red cells during cardiac surgery have more complications during the postoperative course.\textsuperscript{24} A multiple regression analysis identified the intraoperative transfusion of packed red cells as the most important independent variable significantly associated with worse postoperative performance, among the classic risk factors, age and female sex. However, the direct link between packed red cell transfusion and increased postoperative morbidity has yet to be established.
Concluding Remarks

The findings of the present study are important for several reasons. This study shows for the first time that intraoperatively transfused units of packed red cells affect the perioperative release of inflammatory mediators in patients undergoing cardiac surgery. These transfusions affect the well-known systemic inflammatory response to cardiac surgery both by enhancing part of the response and by direct transduction of bioactive substances into the circulation. Thus, our data suggest that the findings of previous studies on the release of inflammatory mediators in response to cardiac surgery and/or the CPB procedure did not take the intraoperative administration of packed red cell transfusions into account need to be reconsidered.

In addition, we show that the intraoperative administration of allogeneic packed red cells in cardiac surgery coincided with increased postoperative morbidity. Because packed red cells contain considerable amounts of BPI, as was demonstrated in this study, other neutrophil granule proteins, such as elastase, cathepsin G, and highly toxic defensins, may also be present in transfusion products. Future studies should reveal whether the administration of these bioactive substances through blood transfusions directly affects postoperative morbidity.

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