Newly Developed Immobilized Polymyxin B Fibers Improve the Survival of Patients with Sepsis

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Newly Developed Immobilized Polymyxin B Fibers Improve the Survival of Patients with Sepsis

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Key Words
Septic shock  Endotoxin  Hemoperfusion  Randomized clinical trial

Abstract
Background: Sepsis and septic shock are still major causes of morbidity and mortality in spite of the availability of powerful and broadly active antibiotics. Methods: A prospective, open and randomized trial of the effect of immobilized polymyxin fibers (PMX-F) on the survival of patients with sepsis throughout a follow-up period of 28 days or until discharge, if earlier, was carried out. Ninety-eight patients were included who met at least 4 of the criteria for systemic inflammatory response syndrome due to infection. The patients were classified into three groups based on their Acute Physiology and Chronic Health Evaluation (APACHE) II score. Results: The overall survival rate was significantly improved by using PMX-F compared to the control group (41 vs. 11%) (p = 0.002). In patients with an APACHE II score less than 20, treatment with PMX-F was shown to improve outcome (65 vs. 19%) (p = 0.01). In cases of more severe sepsis with an APACHE II score of 20–29, PMX-F still maintained efficacy in improving outcome (40 vs. 11%) (p = 0.04). However, PMX-F treatment did not improve the survival rate in patients with an APACHE II score of greater than 30 (survival rate 7 vs. 0%) (p = 0.59). Conclusion: From these results, it is concluded that treatment with PMX-F in patients with sepsis is effective and prolongs the survival rate when applied at an early stage of sepsis. However, in severe sepsis, this therapy does not improve the survival rate.

Introduction
Sepsis and septic shock remain important causes of morbidity and mortality in spite of the availability of high-efficacy antibiotics [1, 2]. This situation may be related to several factors, such as improvement of life-support technology, usage of invasive medical procedures and so on. There have been many clinical trials using new drugs to treat sepsis, including substances which neutralize bacterial toxins and antagonize potentially harmful host mediators [3–9]. Endotoxin induces an inflammatory response that causes multiple organ failure and death when it is present in excess amounts. Experimental observations have supported the concept that endotoxin-directed therapies can benefit patients with septic shock [10–14]. However, no clinical trials using polyclonal coreactive antiserum or immunoglobulin to prevent or treat gram-negative sepsis have thus far shown benefits.
From these results, the anticytokine approach to sepsis has been challenged as being without beneficial effects. This is probably due to the fact that determining when a cytokine-mediated inflammatory event is harmful or beneficial is difficult clinically. Few clinical trials in humans have been published, although many studies in animal models of infection have described the efficacy of tumor necrosis factor antagonists and IL-1 antagonists in the treatment of sepsis [15–17].

In light of this situation, it is possible that the removal of endotoxin could represent a valuable treatment strategy for septic shock. Recently, polymyxin fibers (PMX-F) immobilized in a column have been developed [18–20]. Preliminary clinical trials revealed that of 16 patients with septic multiple organ failure treated with PMX-F, 9 were alive 2 weeks after the therapy and 7 were discharged from the hospital alive [21]. This encouraging study prompted us to apply PMX-F to patients with sepsis. In the present study, patients with systemic inflammatory response syndrome (SIRS) due to infection were classified according to their Acute Physiology and Chronic Health Evaluation (APACHE II) score [22] and randomly assigned to two groups. One group was treated with PMX-F and the other was treated with conventional support therapy for 4 weeks.

**Patients and Methods**

**Study Design**

All patients received regular antibiotic therapy and other supportive treatment and were randomly assigned to a group with or without PMX-F treatment. The primary end point was mortality from all causes on day 28 after the PMX-F procedure.

**Selection of Patients**

Patients with a clinical diagnosis of sepsis, severe sepsis and septic shock according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/ACCM) Consensus Conference were enrolled in the study [2]. The criteria for inclusion in the study were the following findings within the previous 24 h: (1) at least 3 of the following signs of a systemic inflammatory response: hyperthermia or hypothermia (temperature >38°C or <36°C), tachycardia (>90 beats/min), tachypnea (>20 breaths/min) or PaCO₂ less than 32 mm Hg or patient mechanically ventilated, and white blood cell count greater than or equal to 12.0 × 10^9/liter or less than 4.0 × 10^9/liter or 10% or more immature neutrophils, and (2) hypotension despite adequate fluid resuscitation [systolic blood pressure <90 mm Hg, mean arterial pressure <65 mm Hg, or the need for vasopressors (except <5.0 μg of dopamine/kg/min)], and these symptoms were possible as a result of infection. Patients who were less than 18 years old, pregnant or organ transplant recipients and those with hemorrhagic or cardiogenic shock were not enrolled. Patients were not eligible if informed consent from the patient's family was not granted, if they were experiencing acute organ transplant rejection, if they had underlying diseases in addition to the sepsis syndrome so severe that the patient was not expected to survive 3 months after the procedure or, finally, if they were in a chronic vegetative state.

**Design of PMX-F**

The PMX-F cartridge is 225 mm in length and 49 mm in diameter. The priming volume is 135 ml. Polymyxin B is immobilized covalently on the surface of a polystyrene-derived fibrous carrier. As the carrier, the fibrous material is composed of polypropylene-reinforced conjugated fibers. The knitted fabric of polymyxin fiber is rolled up and embedded in the cartridge case as a structural component of the absorbent. Polymyxin fiber effectively adsorbed synthetic lipid A by the Limulus amoebocyte lysate assay.

**Direct Hemoperfusion**

Access to blood for direct hemoperfusion (DHP) with PMX-F adsorbent therapy was achieved via a double-lumen catheter inserted into the femoral vein of each patient by Seldinger's method. Immediately after assuring that the patients met the criteria of SIRS with infection, DHP with PMX-F was started. The time span between diagnosis and initiation of PMX-F treatment was usually less than 3 h. DHP was carried out for 4 h at a flow rate of 80–100 ml/min through a venousous catheter similar to that used for acute dialysis. The anticoagulant was nafamostat mesilate (Torii Co. Ltd., Tokyo, Japan) and the usual doses were between 30 and 50 mg/h.

DHP with PMX-F was performed once or twice, depending on the patient's condition.

Decisions concerning antimicrobial drug therapy, supportive care and surgical intervention were made by the patients' attending physicians and were not dictated by the study protocol.

**Evaluation of the Patients**

Patients were followed for 28 days or until death. An APACHE II score was calculated at entry into the study. Patients were stratified according to the severity of illness at baseline as measured by the overall score on the APACHE II evaluation [22]. In this study, patients with sepsis, severe sepsis and septic shock were all included. The reason why we did not classify the patients according to the definition of sepsis proposed by the ACCP/SCCM Consensus Conference was that we included gram-negative-infected patients who were critically ill due to other disease processes. If the mean blood pressure of patients remained less than 80 mm Hg and/or the dose of inotropic agents was not decreased, DHP with PMX-F was repeated once after the first treatment. A third treatment was not carried out in any of the patients.

The primary source of infection, the causative pathogen and the adequacy of antimicrobial therapy were determined in a blinded fashion by a specialist in the microbiology section.

Gram-negative sepsis was considered to be present at study entry when a culture of blood or body fluid from a site of suspected infection obtained from 2 days before to 2 days after the day of study entry grew a gram-negative organism. In a small number of patients, no infection site was found in spite of an aggressive search for bacterial infection. However, in those patients, gram-negative infection was mostly suspected on the basis of high fever and an increased number of white blood cells with a leftward shift of the differential count.
Table 1. Demographic characteristics of the patients with systemic bacteremia and septic shock with multiple organ failure

<table>
<thead>
<tr>
<th>Group 1 PMX-F(+)</th>
<th>Group 2 PMX-F(-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>54</td>
</tr>
<tr>
<td>Age, years</td>
<td>61±2</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>33:21</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
</tr>
<tr>
<td>Recent surgery</td>
<td>20</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>8</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>4</td>
</tr>
<tr>
<td>Neoplasma</td>
<td>4</td>
</tr>
<tr>
<td>None</td>
<td>8</td>
</tr>
</tbody>
</table>

Clinical and Laboratory Evaluation

Vital signs were recorded frequently during the first 72 h, then every 8 h through to day 7. Mean blood pressure was recorded continuously from a catheter in the brachial artery using a modified Oxford Medilog device before, during and 12 h after PMX-F treatment. Physical examinations and the results of laboratory tests (serum albumin, alkaline phosphatase, total bilirubin, serum urea nitrogen, calcium, chloride, carbon dioxide, creatinine, glucose, potassium, total protein, aspartate transaminase, sodium, uric acid, complete blood cell count including differential and platelet count, prothrombin time, partial thromboplastin time, fibrin split products, urinalysis with microscopic examination and arterial blood gas) were recorded at entry and on days 3, 7, 14 and 28. Serum endotoxin was assayed by the Endospecy method [21]. The normal upper limit was 9.8 pg/ml [21].

Statistical Analysis

All data were expressed as mean ± SD except survival rate. Demographic and baseline characteristics were analyzed using the Wilcoxon test [23, 24] to assess the comparability of the groups with respect to factors possibly related to the outcome. Statistical comparisons within groups were conducted by the use of ANOVA for repeated measures, followed by the Newman-Keuls test. Student's unpaired t test was used for comparisons between groups. The effects of PMX-F on serum endotoxin were compared by paired t test and comparisons between the groups were carried out by unpaired t test. Linear regression analysis was used to assess the relationship between the change in APACHE II scores and the survival time, and a comparison between regression models was made using the t-ratio method [25].

To analyze the difference in mortality over the 28-day period after therapy, Kaplan-Meier survival curves [26] were constructed for the two study groups and compared by the Cochran-Mantel-Haenszel test. A p value of less than 0.049 was considered significant.

Results

Of all the patients enrolled, 54 received PMX-F and 44 were treated without PMX-F. The treatment and non-treatment groups were well balanced with respect to demographic characteristics and underlying diseases (table 1), the distribution of anatomical sources of bacteremia (table 2) and causative organisms (table 3). As

Table 2. Source of gram-negative bacteremia and septic shock

<table>
<thead>
<tr>
<th>Source</th>
<th>PMX-F(+) (n = 54)</th>
<th>PMX-F(-) (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Intraabdominal site</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Other operation site</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3. Gram-negative bacteria isolated from blood culture examination

<table>
<thead>
<tr>
<th>Organism</th>
<th>PMX-F(+) (n = 54)</th>
<th>PMX-F(-) (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>None</td>
<td>20</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 4. Distribution of APACHE II score, its mean and survival rate after 28 days

<table>
<thead>
<tr>
<th>APACHE II score</th>
<th>PMX-F(+) (n = 54)</th>
<th>PMX-F(-) (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>average of APACHE II scores</td>
<td>average of APACHE II scores</td>
</tr>
<tr>
<td></td>
<td>survival rate (day 28), %</td>
<td>survival rate (day 28), %</td>
</tr>
<tr>
<td>&lt;20</td>
<td>20</td>
<td>14±3</td>
</tr>
<tr>
<td>20-29</td>
<td>20</td>
<td>26±3</td>
</tr>
<tr>
<td>&gt;30</td>
<td>14</td>
<td>31±1</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>22±7</td>
</tr>
</tbody>
</table>

Sepsis and Polymyxin Fibers Immobilized in a Column

shown in table 4, the patients with gram-negative bacteremia were severely ill when they entered the study and there were no significant differences in the APACHE II scores between the groups.

Antibiotic therapy was judged to be adequate when the patient received an antibiotic to which each isolated organism was sensitive. This was the case in 65% of the control patients and 69% of the patients treated with

Fig. 1. Correlation between APACHE II scores (x axis) and survival time (y axis) in patients with ($y = 39.571 - 1.099x; r^2 = 0.486$) or without ($y = 21.567 - 0.582x; r^2 = 0.224$) PMX-F treatment. PMX-F treatment improved the survival rate.

Fig. 2. Kaplan-Meier analysis of survival in patients with sepsis receiving PMX-F treatment or supportive care only. An intention-to-treat analysis of mortality from all causes at 28 days by the Cochran-Mantel-Haenszel test showed a significant reduction in mortality in patients treated with PMX-F. a All patients with septic shock ($n = 98$). b Patients with mild sepsis (APACHE II score less than 20) ($n = 36$). c Patients with moderate sepsis (APACHE II score between 20 and 29) ($n = 38$). d Patients with severe sepsis (APACHE II score greater than 30) ($n = 24$).
PMX-F. The survival rate of all patients at 28 days was 11% for those without PMX-F and 41% for those with PMX-F treatment.

Pretreatment APACHE II scores were highly correlated with death among the patients given supportive therapy only in all populations examined (fig. 1) (with PMX-F, $r = 0.697$, $p < 0.0001$; without PMX-F, $r = 0.473$, $p < 0.001$). In order to determine the effects on patient survival of the severity of sepsis, the patients were divided into three categories according to their APACHE II scores. PMX-F significantly improved the survival rate by 30% in the whole group of 98 patients. By 28 days after the initiation of PMX-F, there had been 32 deaths among the 54 patients treated with PMX-F (survival rate 41%) and 39 deaths among the 44 not treated with PMX-F (survival rate 11%). The Kaplan-Meier survival curves show that the reduction in mortality was evident as early as the first day after treatment, was sustained throughout the entire 28-day period of evaluation and was significant ($p = 0.002$) (fig. 2a).

A significant reduction in mortality among moderately severely ill and less severely ill patients who were treated with PMX-F was found; however, in advanced severely ill patients, PMX-F failed to reduce mortality compared to nontreated patients. In less severely ill patients (APACHE II score less than 20), treatment with PMX-F showed a significant and maintained reduction in mortality from the first day after the start of treatment and this remained so. By day 28, 13 of 20 patients had survived with PMX-F treatment (survival rate 65%). Without PMX-F, even in less severely ill patients, only 3 of 16 patients survived to day 28 (survival rate 19%) (fig. 2b) ($p = 0.01$). In moderately severely ill patients (APACHE II score between 20 and 29), treatment with PMX-F resulted in a significant improvement in mortality. Eight of 20 patients treated with PMX-F survived, but only 2 of 18 patients survived without PMX-F (fig. 2c) ($p = 0.04$). However, in severely ill patients (APACHE II score more than 30), all patients died after 12 days without PMX-F and only 1 of 14 patients survived to day 28 even with PMX-F treatment. There were no significant differences between these two groups (fig. 2d) ($p = 0.59$).

PMX-F treatment produced a significant reduction in serum levels of endotoxin from 38.6 ± 5.7 to 21.4 ± 2.0 pg/ml in all patients ($p = 0.006$). In advanced severely ill patients, PMX-F did not decrease serum levels of endotoxin significantly; however, in both less severely and severely ill patients, they were reduced significantly by PMX-F treatment ($p < 0.01$ and $p < 0.04$, respectively) (fig. 3).

PMX-F treatment increased the mean blood pressure from 81 ± 6 to 104 ± 4 mm Hg in less severely ill patients ($p < 0.005$) and from 78 ± 2 to 94 ± 4 mm Hg in severely ill patients ($p < 0.001$); however, it did not change the mean blood pressure of advanced severely ill patients (75 ± 3 to 75 ± 4 mm Hg) (fig. 4).
There were no serious adverse effects of PMX-F in the course of the study. Detailed evaluation of laboratory values revealed no abnormality that was attributable to therapy.

Discussion

The first aim of this study was to examine the efficacy of treatment with immobilized PMX-F in patients with sepsis. Although current definitions restrict the classification of 'severe sepsis' to patients with documented infection, we applied PMX-F to randomly assigned patients with clinically suspected severe sepsis.

All patients were classified according to their APACHE II score. This study was carried out in one university hospital, because hospital size, adjunctive therapy, usage of an intensive care unit and other factors would be expected to influence the rates of mortality if patients with severe sepsis from different centers were investigated.

The APACHE II scoring system has been used widely to predict the outcome as well as to provide an estimate of the likelihood of survival of severely ill patients [22]. In the present study, regardless of treatment with PMX-F, the APACHE II scores correlated significantly with the survival of the enrolled patients.

Hanasawa et al. [18] clearly demonstrated for the first time in 1989 that PMX-F treatment succeeded in prolonging the survival time in dogs with Escherichia coli-induced sepsis. Moreover, 2 of 5 dogs showed complete recovery from septic shock, while all dogs in the control group died within 18 h. Subsequently, in 1994, Aoki et al. [21] from the same group reported their results with treatment using hemoperfusion with PMX-F in 16 patients. Nine of these patients remained alive 2 weeks after receiving this therapy and 7 patients could be discharged from the hospital alive. They showed that PMX-F treatment was able to statistically significantly reduce the serum levels of endotoxin from 76 ± 95 to 21 ± 7 pg/ml. From their studies, it is indicated that the removal of endotoxins using PMX-F is potentially effective for the treatment of patients with severe sepsis. In the present study, PMX-F treatment significantly reduced the serum levels of endotoxin in less severely as well as severely ill patients. In these patients, PMX-F significantly improved the survival rate. Recently, Ebihara et al. [27] clearly demonstrated that PMX-F significantly decreased blood endotoxin levels, associated with a remarkable improvement in survival rate. Moreover, that group provided scientific evidence that treatment with PMX-F attenuates the increased plasma levels of thrombomodulin and von Willebrand factor in patients with septic shock [28]. Recently, Kodama et al. [29] clearly demonstrated results similar to our present data. From these data, combined with the present findings, it can be seen that the major impact of PMX-F on patients suffering from severe sepsis is likely to be attributable to the elimination of endotoxin.

There have been several clinical trials investigating the treatment of sepsis and showing no significant survival benefits [3–9]. The comprehensive meta-analysis by Lefering and Neugebauer [30] concluded that patients with septic shock derive no overall benefit from corticosteroid therapy. As well as corticosteroid hormones, several pharmacological interventions for the treatment of patients with sepsis and/or septic shock, such as E5 (a murine monoclonal IgM antibody raised against the E5 mutant of E. coli O111:B4) [8, 31] and p55 tumor necrosis factor receptor fusion protein [4], have demonstrated their lack of clinical efficacy. In contrast to these substances previously applied for the treatment of sepsis, PMX-F is supposed to directly absorb endotoxin in the blood [18, 32, 33]. It is therefore worthwhile examining the clinical effects of PMX-F. In the present clinical trial, the mortality rates were similar to those of previous clinical trials, ranging from 22 to 50% [1]. Comparable reductions in mortality rate from 89 to 59% were observed with PMX-F in the present trial. Treatment with PMX-F showed efficacy in the patients with lower APACHE scores. A prospective epidemiological study of SIRS and related conditions provided evidence of a clinical progression from SIRS to sepsis to severe sepsis and septic shock [34]. In this clinical trial, the mortality of patients with septic shock was not improved after treatment with PMX-F. It is possible that in septic shock, a multitude of endogenous inflammatory mediators activated in the progression of sepsis produce downstream processes that can no longer be inhibited by neutralizing endotoxin.

Aoki et al. [21] demonstrated that treatment with PMX-F was still effective at a much later stage when patients did not respond to other treatment methods, as well as at an earlier time. The main reason why no significant effects of PMX-F treatment were observed in patients with severe septic shock in the current clinical trial remains unknown. In the review of PMX-F by Jaber and Pereira [19], it was proposed that the early initiation of PMX-F may halt the sepsis syndrome at an earlier stage, and the reason that the mortality data remain similar to historical septic patients may be partly a result of the application of PMX-F too late in advanced stages of sep-
sis. In addition to the severity of sepsis, the influences of bacterial organisms on the beneficial effects of PMX-F should be considered. However, according to the results of a study by Rangel-Frausto et al. [34], there were equal numbers of patients who appeared to have sepsis, severe sepsis and septic shock but who nonetheless had negative cultures. In the present study, the patients with an APACHE score greater than 30 consisted of both culture-positive and culture-negative individuals. It is therefore unlikely that the outcome of PMX-F-treatment is influenced by a positive culture. Moreover, in their preliminary study, the patients enrolled were not classified according to their APACHE score, and therefore the possibility that the severity of illness of the subjects was different cannot be excluded [34].

The effect of some cytokines, such as tumor necrosis factor, is reported to be potentially enhanced in the presence of a small amount of endotoxin. Also, the toxicity of toxic shock syndrome toxin-1 has been shown to be increased 50,000-fold when endotoxin is present [35]. These findings indicate that the removal of a small amount of endotoxin by treatment with PMX-F may be effective. Indeed, in the present study as well as the previous reported results, removal of endotoxin was an important factor in the improvement of sepsis syndrome. In the present study, because we did not measure the serum levels of cytokines such as tumor necrosis factor, interleukin-6, interleukin-1 and so on, it cannot be excluded that the elimination of these factors (which have been suggested to be effective during continuous hemofiltration in patients with sepsis) may contribute to the success of treatment with PMX-F [19].

Treatment with PMX-F may have two major drawbacks in clinical practice. Firstly, it is necessary to draw blood for DHP with PMX-F adsorbent therapy. During this therapy, approximately 100 ml of blood circulates extracorporeally. To apply this technique, a double-lumen catheter needs to be inserted into the femoral vein by Selinger's method. Secondly, anticoagulant therapy is needed to apply this treatment. Compared to therapy with the infusion of agents that bind to and neutralize endotoxin, treatment with PMX-F needs manpower, machines and catheters. This may result in an economical constraint to the application of this therapy. Up to now, however, there have been few successful methods for treating patients with sepsis or septic shock. Therefore, for the time being, this method will be helpful and valuable for the improvement of survival of patients with severe sepsis.

In conclusion, treatment with PMX-F in patients with sepsis is effective and prolongs the survival rate when it is applied at an early stage of sepsis. However, in the advanced stage of sepsis, this therapy does not improve the survival rate.

Acknowledgment

We thank Professor Masashi Kodama (Department of Surgery, Shiga Medical School, Shiga, Japan) for excellent advice.

References

The mortality rate due to sepsis and multiple organ failure in intensive care units is still dramatically high. In spite of the most recent therapeutic advances in critically ill patients suffering from multiple organ dysfunction, the outcome of the septic syndrome is still unfavourable and the impact of new technologies seems to be rather negligible. Very recently, an interesting series of papers has pointed out the potential benefits induced by continuous renal replacement therapies, not only as a method for blood purification, but also as a potential tool to protect from the ‘cytokine storm’ induced by the septic syndrome. In particular, the rationale for extracorporeal therapies in these circumstances would be the possible reduction or at least modulation of the proinflammatory disorder created by the presence of endotoxin and soluble mediators of inflammation in the patient's blood. As mentioned, the proinflammatory cascade generally starts with the bacterial invasion of the host. Then, the endotoxin-mediated stimulation of monocytes generates a spillover of proinflammatory mediators into the circulation.


thus producing systemic effects such as permeabilization of the endothelium and shock. Under such circumstances, the addition to the extracorporeal circuit of new components able to remove circulating endotoxin and proinflammatory mediators could represent an enormous advantage with the possibility of affecting the entire course of the syndrome. In this field, this paper seems to offer hope of a new approach to the treatment of the septic syndrome. The difference in outcome observed in the polymyxin B-treated group in comparison to the controls is remarkable. The time of application of this adjunctive therapy seems to be crucial in preventing the major derangement caused by endotoxemia. If these results were to be confirmed on a larger scale, this might really represent an important step towards the improvement of morbidity and mortality in critically ill patients at risk for septic shock and multiple organ failure. The effects of this therapy on patients already suffering from septic symptoms or shock still need to be evaluated. However, since sepsis is not a single-shot pathologic condition and multiple insults may occur over the course of the syndrome, the efficacy of polymyxin B-coated cartridges may become evident also in more advanced stages of the syndrome. Finally, continuous renal replacement therapies associated with this adsorbent technique may be very efficient and produce incredible results, but if the original cause of the syndrome is not removed, the patient will remain in a state of high risk and mortality may not be influenced.

Continuous renal replacement therapies can be a very important life support resource, but they cannot be a remedy for bad surgery or organic diseases.

Claudio Ronco, Vicenza