Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock
The EUPHAS Randomized Controlled Trial

Dinna N. Cruz, MD, MPH

Massimo Antonelli, MD

Roberto Fumagalli, MD

Francesca Foltran, MD

Nicola Brienza, MD, PhD

Abele Donati, MD

Vincenzo Malcangi, MD

Flavia Petrini, MD

Giada Volta, MD

Franco M. Bobbio Pallavicini, MD

Federica Rottoli, MD

Francesco Giunta, MD

Claudio Ronco, MD

S EVERE SEPSIS AND SEPTIC SHOCK ARE common problems in the intensive care unit (ICU) and carry a high mortality. Endotoxin, one of the principal components on the outer membrane of gram-negative bacteria, is considered relevant to their pathogenesis. High levels of endotoxin activity are associated with worse clinical outcomes.[1] However, effectiveness of endotoxin-targeted therapy is still controversial.[2,3]

Polymyxin B, an antibiotic with high affinity for endotoxin, has been bound and immobilized to polystyrene fibers in a medical device for hemoperfusion. This device can effectively bind endotoxin both in vitro and in vivo and could potentially interrupt the biological cascade of sepsis.[4] In a systematic review,[5] direct hemoperfusion with the

See also p 2496 and Patient Page.

Context Polymyxin B fiber column is a medical device designed to reduce blood endotoxin levels in sepsis. Gram-negative–induced abdominal sepsis is likely associated with high circulating endotoxin. Reducing circulating endotoxin levels with polymyxin B hemoperfusion could potentially improve patient clinical outcomes.

Objective To determine whether polymyxin B hemoperfusion added to conventional medical therapy improves clinical outcomes (mean arterial pressure [MAP], vasopressor requirement, oxygenation, organ dysfunction) and mortality compared with conventional therapy alone.

Design, Setting, and Patients A prospective, multicenter, randomized controlled trial (Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis [EUPHAS]) conducted at 10 Italian tertiary care intensive care units between December 2004 and December 2007. Sixty-four patients were enrolled with severe sepsis or septic shock who underwent emergency surgery for intra-abdominal infection.

Intervention Patients were randomized to either conventional therapy (n=30) or conventional therapy plus 2 sessions of polymyxin B hemoperfusion (n=34).

Main Outcome Measures Primary outcome was change in MAP and vasopressor requirement, and secondary outcomes were PaO_2/FIO_2 (fraction of inspired oxygen) ratio, change in organ dysfunction measured using Sequential Organ Failure Assessment (SOFA) scores, and 28-day mortality.

Results MAP increased (76 to 84 mm Hg; $P=.001$) and vasopressor requirement decreased (inotropic score, 29.9 to 6.8; $P<.001$) at 72 hours in the polymyxin B group but not in the conventional therapy group (MAP, 74 to 77 mm Hg; $P=.37$; inotropic score, 28.6 to 22.4; $P=.14$). The PaO_2/FIO_2 ratio increased slightly (235 to 264; $P=.049$) in the polymyxin B group but not in the conventional therapy group (217 to 228; $P=.79$). SOFA scores improved in the polymyxin B group but not in the conventional therapy group (change in SOFA, −3.4 vs −0.1; $P<.001$), and 28-day mortality was 32% (11/34 patients) in the polymyxin B group and 53% (16/30 patients) in the conventional therapy group (unadjusted hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.20-0.94; adjusted HR, 0.36; 95% CI, 0.16-0.80).

Conclusion In this preliminary study, polymyxin B hemoperfusion added to conventional therapy significantly improved hemodynamics and organ dysfunction and reduced 28-day mortality in a targeted population with severe sepsis and/or septic shock from intra-abdominal gram-negative infections.

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Author Affiliations are listed at the end of this article.
Corresponding Author: Claudio Ronco, MD, Department of Nephrology, Dialysis, and Transplantation, St Bortolo Hospital, Viale Rodolfi 37, 36100 Vicenza, Italy (cronco@goldnet.it).
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polymyxin B device appeared to have favorable effects on mean arterial pressure (MAP), vasopressor use, PaO$_2$/FIO$_2$ (fraction of inspired oxygen) ratio, and mortality. However, the conclusions were limited by the low methodological quality of the available studies and heterogeneous study populations; therefore, the authors argued the need for further rigorous study of this therapy. In a small European pilot study,[6] polymyxin B was shown to improve cardiac and renal dysfunction due to sepsis or septic shock but had no effect on mortality. More recently, another small randomized study[7] demonstrated favorable effects of polymyxin B on renal tubular cell structure and function.

Septic shock of intra-abdominal origin is likely to be due to gram-negative bacteria or mixed pathogens and consequently associated with high endotoxin levels. Thus, it represents a condition in which endotoxin-targeted therapy may be of particular benefit.[3] We performed a randomized controlled trial (RCT) in a targeted population of patients with septic shock who underwent emergency surgery for intra-abdominal infection. Our hypothesis was that polymyxin B hemoperfusion would be associated with better patient outcomes, such as improved survival, better hemodynamic and oxygenation status, and mitigation of organ dysfunction.

METHODS
Patients

Our prospective RCT (Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis [EUPHAS]) was conducted in 10 Italian ICUs (St Bortolo Hospital, Vicenza; Catholic University of Sacred Heart and Policlinico Umberto I of Rome, Rome; University of Pisa, Pisa; University of Bari, Bari; Polytechnical University of Marche, Ancona; University of Chieti-Pescara, Chieti; Policlinico S. Orsola-Malpighi Hospital, Bologna; S. Martino University Hospital, Genova; and Riuniti Hospital, Bergamo) between December 2004 and December 2007. The ethics committees for each center approved the study protocol, and informed consent was obtained from each patient or the patient's relative or surrogate.

Patients were eligible for enrollment if they had severe sepsis or septic shock due to intra-abdominal cavity infection requiring emergency abdominal surgery. Severe sepsis and septic shock were defined according to the consensus definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.[8] Exclusion criteria included aged younger than 18 years, pregnancy, inclusion in other ICU studies within the last month, organ transplantation in the last year, terminally ill patients classified as "do not resuscitate," history of sensitivity to polymyxin B or to anticoagulant (heparin), uncontrolled hemorrhage within the last 24 hours, severe granulocytopenia (leukocyte count of <500/μL), and severe thrombocytopenia (platelet count of <30 000/μL).

Randomization

Eligible patients were randomly assigned within 6 hours of their surgery to treatment with either conventional medical therapy alone, according to Surviving Sepsis Campaign[9] guidelines (conventional therapy group), or direct hemoperfusion therapy with polymyxin B in addition to standard therapy (polymyxin B hemoperfusion group). Randomization was performed by a computer-generated (simple random number) scheme stratified by center. The allocation sequence was concealed in sealed envelopes held at a central coordinating center, which was available 24 hours a day throughout the study to answer clinicians' questions about eligibility. Although treatment groups could not be feasibly masked, investigators were unaware of aggregate outcomes during the study. Data analysts were also blinded to the nature of the patients' allocation group.

Procedures

Treatment was started and monitored by the physician responsible for patient care at each center. All centers had longstanding experience with extracorporeal therapy in the ICU setting. Patients randomized to the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard medical therapy. Vascular access was obtained with use of double-lumen venous catheters. Hemoperfusion was performed in the ICU by using an adsorbent column containing 5 mg of polymyxin B per gram of polystyrene fiber (Toraymyxin, Toray Industries, Tokyo, Japan) within 24 hours after abdominal surgery. Hemoperfusion with polymyxin B was performed for 2 hours, and then the second polymyxin B treatment was performed 24 hours after the end of the first treatment. Heparin (unfractionated or low-molecular-weight) was used as the anticoagulant, at the discretion of the treating physician.

Renal replacement therapy (RRT) for acute kidney injury was initiated at the discretion of the responsible physicians. There were no standardized criteria to start or end RRT. When RRT was performed, biocompatible membranes were used; the specific type and surface area were left to physician discretion. Polymyxin B hemoperfusion (as well as RRT, when performed) was performed on different RRT machines throughout the study, depending on availability in the participating centers.

Data Collection

Clinical data were recorded at baseline, at 48 hours, and at 72 hours. Severity of organ dysfunction or failure was expressed by using the Sequential Organ Failure Assessment (SOFA) score (range, 0-24; lower scores indicate better organ function).[10] The delta SOFA[11-13] was used to indicate the change in degree of organ dysfunction after randomization and calculated as the SOFA score at each time point minus the SOFA score at baseline. The dose of vasoactive/vasopressor agents is expressed as the inotropic score,[14,15] a dimensionless variable calculated as:

$$(\text{dopamine dose} \times 1) + (\text{dobutamine dose} \times 1) + (\text{adrenaline dose} \times 100) + (\text{noradrenaline dose} \times 100) + (\text{phenylephrine dose} \times 100),$$

wherein all doses are expressed as

µg/kg/min. This score has also been referred to as the vasopressor score[16] or catecholamine index.[17] In clinical practice, the vasopressor dose is titrated periodically according to the blood pressure. Therefore, a dose-response relationship between vasopressor dose and MAP was used as another surrogate for the degree of hemodynamic impairment. We expressed this dose-response relationship as the vasopressor dependency index, which is calculated as the ratio of inotropic score to MAP; the higher the score, the greater the vasopressor requirement. Patients receiving RRT were assigned a renal SOFA score of 4.

End Points

The primary end points were changes from baseline to 72 hours in MAP and vasopressor requirement. The secondary end points included PaO_2/FIO_2 ratio, change in organ dysfunction (measured by delta SOFA scores), and 28-day mortality. Need for RRT, length of ICU, hospital stay, and all-cause hospital mortality were also reported.

Statistical Analysis

In previous unpublished pilot data on septic shock in one of the participating centers, MAP varied from 60 to 70 mm Hg. A sample size of 120 patients (60 in each group) was calculated to detect an absolute difference of 5 mm Hg in delta MAP between the polymyxin B hemoperfusion group and conventional therapy group, with a power of 80% and 2-sided α = .05. Such a sample size would also have sufficient power to detect a hazard ratio (HR) of 0.50 between the polymyxin B hemoperfusion group and the conventional group.[5] Based on national data on septic shock,[18] a probability of death was estimated to be 55% in the conventional therapy group.

An interim analysis was planned after 30 patients per group had been enrolled and followed up until hospital discharge, based on ethics committee requirements. The predefined stopping rules were based on the HR in the Cox proportional hazards regression
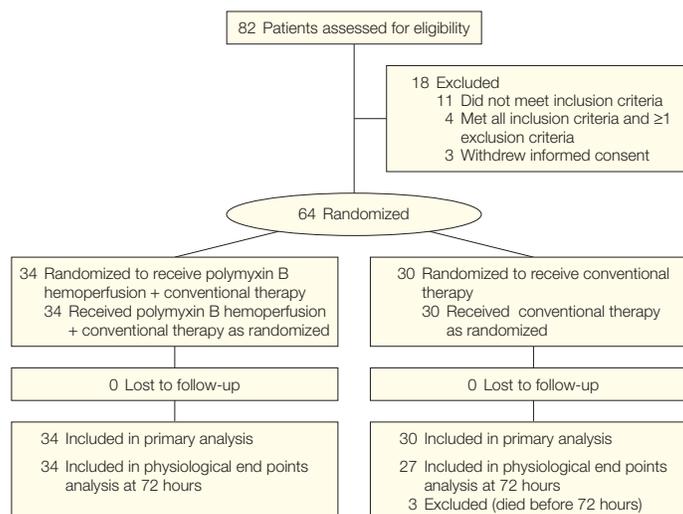
survival model. If polymyxin B was associated with a reduced hazard, the *P* value needed to stop the trial was less than .029 (Pocock value for 1 interim analysis), and if polymyxin B was associated with an increased hazard, the *P* value needed to stop the trial was less than .05.[19-21] Analyses were performed on an intention-to-treat basis.

Categorical variables are presented as proportions and were analyzed by using χ^2 test or Fisher exact test. Continuous variables are presented as means and 95% confidence intervals (CIs). Comparisons of continuous variables between the 2 groups were conducted with *t* test or the Mann-Whitney U test, as appropriate. Comparisons within a single group among different time points (baseline and 72 hours) were performed by using a paired *t* test, Wilcoxon rank sum test, or McNemar test, as appropriate. Multivariable analysis of mortality end points was performed by using Cox proportional hazards regression, adjusting for SOFA score at baseline. Duration of survival was calculated from the date of randomization to the date of death, with survivors censored at hospital discharge. The Cox proportional hazards regression

assumption was checked by using the Schoenfeld test. Data were analyzed with STATA version 9.2 (StataCorp LP, College Station, Texas), with 2-sided $P < .05$ considered statistically significant.

RESULTS

Between December 2004 and December 2007, 64 patients (34 in the polymyxin B hemoperfusion group and 30 in the conventional therapy group) entered the study, and all were followed up until death or hospital discharge, triggering the first interim analysis. The analysis triggered the stopping rule based on a statistically significant reduction in mortality in the polymyxin B hemoperfusion group. Results were discussed with the president of the ethics committee (Internal Institutional Ethical Commission of the coordinating center), who declared it unethical to deprive a potentially beneficial therapy to a group of patients that carry high mortality. The study was thus terminated.

FIGURE 1 shows the trial profile. Baseline characteristics of the study population are shown in TABLE 1. There were no significant differences between the

Figure 1. Patient Flow Diagram of EUPHAS Trial

EUPHAS indicates Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis. Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy.

2 groups. TABLE 2 lists the isolated microorganisms and sites from which they were obtained (7 patients had positive cultures from >1 site). Multiple microorganisms were isolated in 34% of patients. Abdominal surgery was performed for bowel perforation (n=41), intestinal occlusion/resection (n=13), complicated cholecystitis (n=7), intra-abdominal abscess (n=2), and peritonitis not otherwise specified (n=1). There was no significant difference between the 2 groups in terms of indication for abdominal surgery.

Primary End Point

At 72 hours, MAP significantly increased from 76 mm Hg (95% CI, 72-80 mm Hg) at baseline to 84 mm Hg (95% CI, 80-88 mm Hg; P=.001), while inotropic score (an indicator of both catecholamine and dopamine use) significantly decreased from 29.9 (95% CI, 20.4-39.4) at baseline to 6.8 (95% CI, 2.9-10.7) in the polymyxin B hemoperfusion group (P<.001) (TABLE 3). This was not observed in the conventional therapy group (MAP, 74 mm Hg; 95% CI, 70-78 mm Hg; to 77 mm Hg; 95% CI, 72-82 mm Hg; P=.37; and inotropic score, 28.6; 95% CI, 16.6-40.7; to 22.4; 95% CI, 9.3-35.5; P=.14). Consequently, the vasopressor dependency index, an expression of the dose-response relationship between vasopressors and MAP, decreased significantly in the polymyxin B hemoperfusion group (4.3 mm Hg^{-1}; 95% CI, 2.7-5.9 mm Hg^{-1}; to 0.9 mm Hg^{-1}; 95% CI, 0.3-1.5 mm Hg^{-1}; P<.001) but not in the conventional therapy group (4.1 mm Hg^{-1}; 95% CI, 2.3-6.0 mm Hg^{-1}; to 3.3 mm Hg^{-1}; 95% CI, 1.3-5.3 mm Hg^{-1}; P=.26).

Secondary End Points

The secondary end points are shown in Table 3, TABLE 4, and FIGURE 2. A borderline significant improvement in the PaO$_2$/FIO$_2$ ratio in the polymyxin B hemoperfusion group was observed (235; 95% CI, 206-265 at baseline; and 264; 95% CI, 236-292 at 72 hours; P=.049). The PaO$_2$/FIO$_2$ ratio remained unchanged in the conventional therapy group (217; 95% CI, 188-247 at baseline; and 228; 95% CI, 199-258 at 72 hours; P=.79). The delta SOFA scores showed significant improvement of organ failure in the polymyxin B hemoperfusion group (Figure 2). At 72 hours, the polymyxin B hemoperfusion group had a greater reduction com-

Table 1. Baseline Characteristics of the Treatment Groups[a]

| Characteristics | Mean (95% Confidence Interval) | | P Value |
	Polymyxin B Hemoperfusion (n = 34)	Conventional Therapy (n = 30)	
Age, y	61 (57-66)	67 (61-72)	.09
Male sex, No. (%)	24 (71)	18 (60)	.53
APACHE II score	21 (19-23)	20 (18-23)	.86
SOFA score	11 (10-12)	9 (8-11)	.07
Mean arterial pressure, mm Hg	76 (72-80)	74 (70-78)	.40
Noradrenaline, μg/kg/min	0.27 (0.17-0.36)	0.24 (0.13-0.36)	.70
Dopamine, μg/kg/min	3.1 (1.7-4.4)	4.6 (2.9-5.6)	.13
Inotropic score	29.9 (20.4-39.4)	28.6 (16.6-40.7)	.85
Vasopressor dependency index, mm Hg^{-1}	4.3 (2.7-5.9)	4.1 (2.3-6.0)	.87
White blood cell count, 1000/μL	13.7 (11.4-16.0)	11.4 (9.0-13.8)	.12
PaO$_2$/FIO$_2$	235 (206-265)	217 (188-247)	.53
Diuresis, mL/h	66 (50-90)	87 (59-116)	.22
Creatinine, mg/dL	2.3 (1.7-2.9)	1.7 (1.3-2.2)	.18
Renal replacement therapy, No. (%)	13 (38)	6 (20)	.17

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; FIO$_2$, fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment.
SI conversion: To convert creatinine to μmol/L, multiply by 88.4.
[a]Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy. Range of APACHE II score was 0 to 71, with lower scores indicating better organ function. Range of SOFA score was 0 to 24, with lower scores indicating better organ function. See "Methods" section for formulas for inotropic score and vasopressor dependency index.

Table 2. Isolated Microorganisms by Treatment Group

Organisms and Sites	Polymyxin B Hemoperfusion	Conventional Therapy
Organisms		
Escherichia coli	10	10
Pseudomonas species	7	5
Bacillus species	1	0
Enterococcus species	5	0
Staphylococcus species	3	0
Streptococcus species	1	0
Candida species	6	5
Enterobacter species	4	1
Klebsiella species	1	0
Proteus species	1	3
Corynebacterium species	0	1
Aspergillus species	0	1
Serratia species	0	2
Sites		
Peritoneal, abdominal fluid, drainage	9	10
Blood	16	3
Urine	2	1
Other	2	2
Multiple organisms	13	9
Multiple sites	6	1

Table 3. Physiological End Points by Treatment Group at Baseline and 72 Hours[a]

| | Polymyxin B Hemoperfusion | | | Conventional Therapy | | |
| | Mean (95% CI) | | | Mean (95% CI) | | |
Physiological End Points	Baseline (n = 34)	72 Hours (n = 34)	P Value	Baseline (n = 30)	72 Hours (n = 27)	P Value
Mean arterial pressure, mm Hg	76 (72-80)	84 (80-88)	.001	74 (70-78)	77 (72-82)	.37
Inotropic score	29.9 (20.4-39.4)	6.8 (2.9-10.7)	<.001	28.6 (16.6-40.7)	22.4 (9.3-35.5)	.14
Vasopressor dependency index, mm Hg^{-1}	4.3 (2.7-5.9)	0.9 (0.3-1.5)	<.001	4.1 (2.3-6.0)	3.3 (1.3-5.3)	.26
PaO$_2$/FiO$_2$	235 (206-265)	264 (236-292)	.049	217 (188-247)	228 (199-258)	.79
Renal replacement therapy, No. (%)	13 (38)	15 (44)	.50	6 (20)	8 (30)	.50

Abbreviations: CI, confidence interval; FiO$_2$, fraction of inspired oxygen.
[a] See "Methods" section for formulas for inotropic score and vasopressor dependency index. In the conventional therapy group, 3 patients died before 72 hours (n=27).

pared with the conventional therapy group in terms of total SOFA (mean delta SOFA score, –3.4; 95% CI, –4.4 to –2.4; vs –0.1; 95% CI, –1.7 to 1.5; $P<.001$), cardiovascular SOFA (mean delta SOFA score, –1.7; 95% CI, –2.4 to –1.0; vs –0.7; 95% CI, –1.2 to –0.2; $P=.04$), and renal SOFA (mean delta SOFA score, –0.3; 95% CI, –0.7 to 0.1; vs 0.6; 95% CI, 0.1 to 1.1; $P=.01$). However, the 2 groups were similar in terms of respiratory SOFA (mean delta SOFA score, –0.1; 95% CI, –0.4 to 0.2; vs –0.1; 95% CI, –0.5 to 0.3; $P=.97$).

The 28-day crude mortality was 32% (11/34 patients) in the polymyxin B hemoperfusion group and 53% (16/30 patients) in the conventional therapy group. The unadjusted mortality rates are shown in Table 4 (unadjusted HR, 0.43; 95% CI, 0.20-0.94), and the survival curve is shown in FIGURE 3. With univariable analysis, only treatment group and SOFA score were independently associated with mortality. After adjusting for SOFA score, the polymyxin B hemoperfusion group had a significant reduction in 28-day mortality (adjusted HR, 0.36; 95% CI, 0.16-0.80; $P=.01$). In a further analysis of hospital mortality, 20 of 30 patients (67%) died in the conventional therapy group compared with 14 of 34 patients (41%) in the polymyxin B hemoperfusion group. After adjusting for SOFA score, the polymyxin B hemoperfusion group had a significant reduction in hospital mortality rate (adjusted HR, 0.43; 95% CI, 0.21-0.90;

$P=.026$ [Pocock value for 1 interim analysis, $P<.029$]).

There was no significant change in the proportion of patients receiving RRT at 72 hours in either group (Table 3). The mean number of RRT-free days in the hospital was 31.6 days (95% CI, 24.6-38.6 days) in the polymyxin B hemoperfusion group and 26.7 days (95% CI, 13.4-40.3 days) in the conventional therapy group ($P=.61$). Mean mechanical ventilation-free days in the hospital were similar between the 2 groups (polymyxin B hemoperfusion: 21.4 days; 95% CI, 15.4-27.3 days; vs conventional therapy: 17.0 days; 95% CI, 8.5-25.3 days; $P=.47$). Likewise, there was no significant difference in mean length of stay in the ICU (20.3 days; 95% CI, 15.0-25.5 days; vs 18.3 days; 95% CI, 8.8-27.8 days; $P=.72$) or in the hospital (37.2 days; 95% CI, 29.6-44.8 days; vs 32.0 days; 95% CI, 18.0-46.0 days; $P=.53$).

Adverse Events

During the study, only adverse events in the polymyxin B hemoperfusion

Table 4. All-Cause Mortality Rates by Treatment Group

| | 28 Days | | In-Hospital | |
	Polymyxin B Hemoperfusion	Conventional Therapy	Polymyxin B Hemoperfusion	Conventional Therapy
No. of deaths	11	16	14	20
Time at risk, d	805	491	1265	960
Mortality rate per 100 patient-days, mean (95% CI)	1.4 (0.8-2.4)	3.2 (2.0-5.3)	1.1 (0.6-1.9)	2.1 (1.3-3.2)

Abbreviation: CI, confidence interval.

group were recorded. Cartridge clotting was registered in 4 cases (6%); all cases could be attributed to the low dose of heparin used. Hypotension and tachycardia were reported in 1 case (1.5%) and 2 cases (3%), respectively. No adverse event due to bleeding and no event indicative of neurotoxicity or nephrotoxicity related to polymyxin B were reported.

COMMENT

The effects of polymyxin B hemoperfusion on clinical end points in patients with sepsis have been debated in recent years, in part due to the paucity of high-quality data in this arena. Available studies were highly heterogeneous with regards to patient selection and indication for polymyxin B hemoperfusion therapy, and had suboptimal methodological quality. The results of our study shed light on this controversial matter. In this RCT of surgical patients with septic shock and severe sepsis induced by abdominal sepsis, polymyxin B hemoperfu-

sion therapy was effective in improving 28-day and hospital survival, blood pressure, vasopressor requirement, and degree of organ failure as indicated by the delta SOFA score when added to conventional medical treatment. Observed adverse effects associated with polymyxin B hemoperfusion therapy were minimal and similar to those that would be encountered for any extracorporeal therapy in the ICU.

Our findings are in agreement with those of other studies in diverse populations, which were summarized in a recent meta-analysis.[5] Among 8 RCTs included in this systematic review, the overall relative risk reduction for all-cause mortality with polymyxin B therapy was 50%.[6,8,22-28] Our results were quite similar, in that the polymyxin B hemoperfusion group had an adjusted HR of 0.36 for 28-day mortality and 0.43 for all-cause hospital mortality. The delta SOFA scores were significantly better in the polymyxin B hemoperfusion group (Figure 2), indicating improvement in overall organ function,[10-13] particularly in the cardiovascular component. Improvement in blood pressure and reduction in vasopressor doses have also been demonstrated in other studies.[29,30] In our study, even as the dose of vasoactive agents (indicated by the inotropic score) was reduced, there was a significant increase in MAP in the polymyxin B hemoperfusion group at 72 hours (Table 3). Accordingly, the vasopressor dependency index decreased significantly in the polymyxin B hemoperfusion group but not in the conventional therapy group.

In terms of pulmonary function, there was no significant difference in mechanical ventilation-free days or delta respiratory SOFA score between the 2 groups. Observational studies and case reports have suggested a beneficial effect of polymyxin B therapy on PaO_2/FIO_2 ratio in sepsis, acute lung injury and acute respiratory distress syndrome,[5,31] and acute exacerbation of interstitial pneumonia.[32,33] Differences in patient population, study design, and sample size likely contribute to these discordant results.

In terms of renal dysfunction, the delta renal SOFA score at 72 hours was better in the polymyxin B hemoperfusion group (Figure 2), indicating some improvement in the degree of renal organ dysfunction in this group. However, the proportion of patients treated with RRT was similar between the 2 groups. Earlier studies have demonstrated positive renal effects of polymyxin B therapy. In the RCT of Nakamura et al,[34] a decrease in serum creatinine, albuminuria, and urinary N-acetyl-B-glucosaminidase levels was shown after polymyxin B therapy in patients with severe sepsis. These authors hypothesized that polymyxin B therapy mitigated proximal renal tubular cell damage. More recently, the study by Cantaluppi et al[7] demonstrated that polymyxin B reduces the proapoptotic activity of plasma from septic patients on cultured renal tubular cells, via modulation of Fas upregulation, caspase activity, and Bax/Bcl2 ratio. An improvement in acute kidney injury severity, assessed by Risk-Injury-Failure-Loss-Endstage kidney disease (RIFLE) classification,[35] was also observed in this small study. However, these patients had relatively mild acute kidney injury; at enrollment, none of the patients were receiving RRT. In contrast, 30% of our study population were already receiving RRT at enrollment.

This study to our knowledge is the largest multicenter RCT on direct hemoperfusion with polymyxin B in patients with septic shock and severe sepsis induced by abdominal sepsis. We focused on a very homogenous and ill patient population, likely to have high

Figure 2. Change in SOFA Scores at 72 Hours
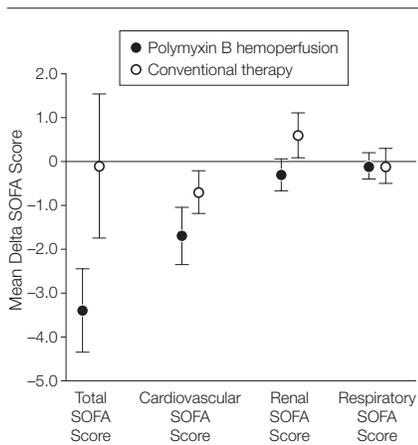
SOFA indicates Sequential Organ Failure Assessment. Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy. Error bars represent 95% confidence intervals. Negative values for delta SOFA scores indicate improvement in organ function, and positive values indicate worsening.

Figure 3. Estimation of Survival Rate According to Treatment Group
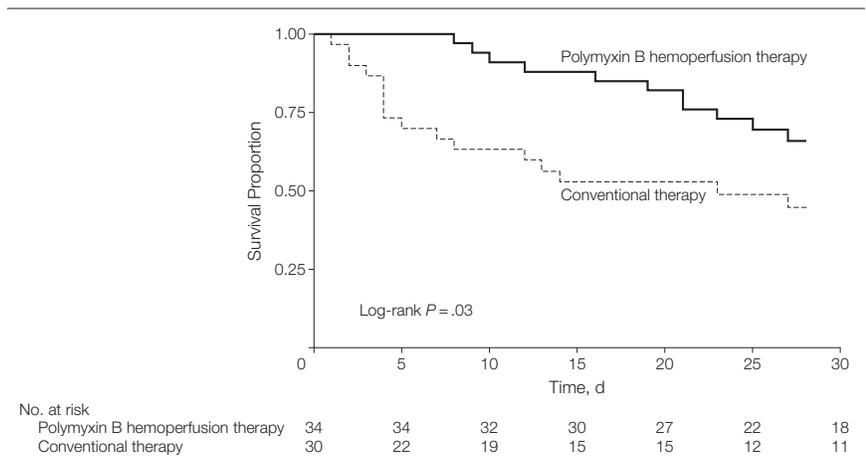
Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy.

endotoxin levels, and in whom definitive source control was possible. Unlike the European pilot study,[6] we excluded elective abdominal surgery cases and performed 2, rather than only 1, polymyxin B hemoperfusion sessions; the use of 2 sessions is more consistent with the large Japanese experience with this device. However, there are limitations to our study. First, although one of the strengths of this study is its highly targeted patient population, this also contributed to slow patient accrual. Second, due to the nature of the study intervention, it was not feasible to blind treating physicians to the patient's allocation group. The data analysts, however, were blinded. Third, the trial was stopped early based on the results of the interim analysis, following accepted standards for stopping.[19-21] The resulting sample size was therefore modest; the results were nonetheless worthy of note and aligned with the results from the meta-analysis.[5] Although smaller studies tend to overestimate the true magnitude of a clinical effect, there nevertheless seems to be a strong biological "signal" of a benefit with polymyxin B therapy. Moreover, we should remark that early stopping itself tends to overestimate the true effect for the factor used in the stopping rule, in this case, mortality. However, even a 20% relative reduction in 28-day mortality, as indicated by the upper end of the 95% CI, would be considered clinically relevant in this highly fatal condition.

We acknowledge other limitations. Although we saw favorable effects of polymyxin B on blood pressure and vasopressor use, we are unable to comment on parameters, such as cardiac output, cardiac index, and systemic vascular resistance, because not all patients had invasive hemodynamic monitoring. However, other studies have already demonstrated improvement in these parameters in other patient populations.[6,36,37] We also acknowledge the inability of the trial to provide definitive answers on the effects of dose, duration, and number of required polymyxin B treatments. Lastly,

we evaluated the effect of polymyxin B in a surgical population with intra-abdominal sepsis, in whom definitive surgical removal of the septic focus was possible; therefore, caution should be exercised in extrapolating our results to sepsis in a medical population. Although polymyxin B therapy reduces endotoxin levels, and thus is capable of modulating the cascade of events in sepsis, it does not directly address the primary event of sepsis (ie, the infection). Therefore, polymyxin B cannot afford a definitive cure, but instead could potentially serve as an adjunct to timely appropriate antibiotic and other medical therapy in severe sepsis.

In conclusion, this preliminary RCT demonstrates that polymyxin B therapy, when added to conventional medical therapy, was effective in improving clinical outcomes in a targeted population of severe sepsis and septic shock due to intra-abdominal infections. Larger multicenter studies are indicated to confirm these encouraging findings in other patient populations. Furthermore, we advocate further studies to explore the use of newer assays for endotoxin activity both for patient selection, as well as guiding the number of hemoperfusion sessions.

Author Affiliations: Department of Nephrology, Dialysis, and Transplantation, St Bortolo Hospital and International Renal Research Institute Vicenza, Vicenza (Drs Cruz and Ronco); Department of Anesthesiology and Intensive Care, Policlinico Gemelli, Catholic University of Sacred Heart, Rome (Dr Antonelli); Department of Anesthesiology and Intensive Care I, Milano Bicocca University, St Gerardo dei Tintori Hospital, Monza (Dr Fumagalli); Department of Surgery, University of Pisa, Pisa (Drs Foltran and Giunta); Department of Emergency and Organ Transplantation, Anesthesia and Intensive Care Unit, University of Bari, Bari (Drs Brienza and Malcangi); Department of Neuroscience, Anesthesia, and Intensive Care, Polytechnical University of Marche, Ancona (Dr Donati); Department of Anesthesia, Intensive Care, and Emergency, University of Chieti-Pescara, Chieti (Dr Petrini); Department of Anesthesiology and Intensive Care, Policlinico S. Orsola-Malpighi Hospital, Bologna (Dr Volta); Department of Intensive Care, S. Martino University Hospital, Genova (Dr Bobbio Pallavicini); and Department of Anesthesiology and Intensive Care, Riuniti Hospital, Bergamo (Dr Rottoli), Italy.

Author Contributions: Dr Ronco had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Antonelli, Giunta, Ronco.
Acquisition of data: Cruz, Antonelli, Fumagalli, Foltran, Brienza, Donati, Malcangi, Petrini, Volta, Bobbio Pallavicini, Rottoli, Giunta, Ronco.
Analysis and interpretation of data: Cruz, Antonelli, Foltran, Brienza, Malcangi, Giunta, Ronco.

Drafting of the manuscript: Cruz, Antonelli, Foltran, Giunta, Ronco.
Critical revision of the manuscript for important intellectual content: Cruz, Antonelli, Fumagalli, Brienza, Donati, Malcangi, Petrini, Volta, Bobbio Pallavicini, Rottoli, Giunta, Ronco.
Statistical analysis: Cruz, Antonelli, Foltran, Giunta.
Administrative, technical, or material support: Giunta, Ronco.
Study supervision: Antonelli, Fumagalli, Giunta, Ronco.
Participating Centers and Investigators: *Department of Nephrology, Dialysis, and Transplantation, St Bortolo Hospital (coordinating center), Vicenza, Italy*: Dinna Cruz, MD, MPH, Alessandra Brendolan, MD, Federico Nalesso, MD, Claudio Ronco, MD; *Department of Intensive Care and Anesthesiology, Policlinico Gemelli, Catholic University of Sacred Heart, Rome, Italy*: Antonella Meraglia, MD, Gabriella Salvatori, MD, Teresa Chilà, MD, Carmela Bonarrigo, MD, Massimo Antonelli, MD; *Department of Surgery, University of Pisa, Pisa, Italy*: Francesca Foltran, MD, Francesco Forfori, MD, Patrizia Cosimini, MD, Francesco Giunta, MD; *Department of Emergency and Organ Transplantation, Anesthesia and Intensive Care Unit, University of Bari, Bari, Italy*: Vincenzo Malcangi, MD, Nicola Brienza, MD, PhD; *Department of Neuroscience, Anesthesia, and Intensive Care, Polytechnical University of Marche, Ancona, Italy*: Abele Donati, MD; *Department of Anesthesia, Intensive Care, and Emergency, University of Chieti-Pescara, Chieti, Italy*: Flavia Petrini, MD; *Department of Anesthesiology and Intensive Care, Policlinico S. Orsola-Malpighi Hospital, Bologna, Italy*: Giada Volta, MD, Gabriela Sangiorgi, MD; *Department of Intensive Care, S. Martino University Hospital, Genova, Italy*: Franco M. Bobbio Pallavicini, MD; *Department of Anesthesiology and Intensive Care, Riuniti Hospital, Bergamo, Italy*: Federica Rottoli, MD, Ivano Riva, MD, Elena Moretti, MD, Mariano Marchesi, MD; *Department of Anesthesiology and Intensive Care, Policlinico Umberto I of Rome, Rome, Italy*: Zaccaria Ricci, MD.

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