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ORIGINAL ARTICLE

Effectiveness of polymyxin B-direct hemoperfusion (PMX-DHP) therapy using a polymyxin B-immobilized fiber column in patients with post-esophagectomy sepsis

Masashi Takahashi · Hiroya Takeuchi · Hirofumi Kawakubo · Rieko Nakamura · Tsunehiro Takahashi · Norihito Wada · Yoshiro Saikawa · Tai Omori · Yuko Kitagawa

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Abstract
Background Post-esophagectomy complications have an extremely poor prognosis. Recently, polymyxin B-direct hemoperfusion (PMX-DHP) therapy using a polymyxin B-immobilized fiber column was reported to be beneficial in gram-negative and/or gram-positive bacterial sepsis. The present retrospective study investigated the effectiveness and safety of PMX-DHP therapy in severe sepsis or septic shock after esophagectomy.
Methods Fifteen severe sepsis or septic shock patients were included. Seven (four, pneumonia; two, anastomotic leakage; and one, reconstructed colon necrosis) patients received 2–5 h of PMX-DHP therapy (PMX-DHP therapy group), whereas 8 (three, pneumonia; three, anastomotic leakage; and two, gastric tube necrosis) received conventional therapy (control group).
Results Length of stay in the intensive care unit (ICU) was significantly shorter in the PMX-DHP therapy group than in the conventional therapy group ($P = 0.040$). In the comparison of pre- and post-PMX-DHP therapy groups, the total Sequential Organ Failure Assessment (SOFA) score, respiratory system score, and P/F ratio improved ($P = 0.0027$, $P = 0.025$, and $P = 0.0087$, respectively) in the post-PMX-DHP therapy group. In the comparison of conventional and PMX-DHP therapy groups, the variations in the total SOFA score, respiratory system score, and P/F ratio improved ($P = 0.019$, $P = 0.0063$, and $P = 0.0015$, respectively) in the PMX-DHP therapy group. Moreover, the respiratory system score was lower ($P = 0.0062$) in the PMX-DHP therapy group at the time of discharge from the ICU. No adverse effects were observed during the course of PMX-DHP therapy.
Conclusions PMX-DHP therapy was safe and effective in improving respiratory and general conditions of patients with severe sepsis and septic shock after esophagectomy and decreased the length of stay in the ICU.

Keywords Esophagectomy · Postoperative complications · Sepsis · Hemoperfusion

M. Takahashi · H. Takeuchi (✉) · H. Kawakubo · R. Nakamura · T. Takahashi · N. Wada · Y. Saikawa · T. Omori · Y. Kitagawa
Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
e-mail: htakeuchi@a6.keio.jp

Introduction

Esophageal cancer is the eighth most common cancer and the seventh largest cause of cancer-related deaths worldwide, with 482,300 new cases and 406,800 deaths reported annually [1]. Esophagectomy with radical lymphadenectomy for esophageal carcinoma is one of the most effective treatments. However, this operative procedure is associated with high rates of morbidity and mortality, particularly in low-volume care centers [2]. Although mortality rates have recently decreased [3, 4], morbidity rates still remain high. Contemporary large-series studies report overall morbidity rates of 26–67 %, with major morbidity in 26–36 % patients undergoing surgery [5–10]. Pulmonary complications are almost uniformly recognized as the most frequent complication following esophagectomy and are reported at 13–38 % [11–22]. Anastomotic leak is also a major complication and is reported at 3–25 % [23–26]. The majority of patients who develop a major complication after esophagectomy frequently proceed to sepsis and have a poor prognosis. These complications can result in prolonged ventilator requirements, extended stays in the

intensive care unit (ICU), reoperation, and increased mortality [27].

Polymyxin B-direct hemoperfusion (PMX-DHP) therapy is a highly effective method for treating sepsis to remove plasma endotoxins produced by gram-negative bacteria [28–30]. However, several studies have also reported that this therapy is beneficial in patients with gram-positive bacterial infection [29, 30] or with endotoxin-negative infection [31]. PMX-DHP therapy reportedly improved pulmonary oxygenation in patients with acute respiratory distress syndrome (ARDS), which is pathologically characterized by diffuse alveolar damage [31–33].

However, little is known about the efficacy of PMX-DHP therapy in patients with sepsis due to complications after esophagectomy. Here we hypothesized that PMX-DHP therapy is beneficial in such a patient population. In this study, we retrospectively evaluated the efficacy of PMX-DHP therapy in patients with post-esophagectomy sepsis at our institution.

Methods

Patients

Between January 2001 and December 2012, 388 esophageal carcinoma patients underwent esophagectomy at the Department of Surgery, Keio University School of Medicine. Severe sepsis or septic shock was observed in 15 patients (3.9 %); these patients were included in this study. Sepsis was defined as suspected infection in the presence of two or more systemic inflammatory response syndrome criteria. Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension. Hypoperfusion abnormalities were considered to include lactic acidosis, oliguria, and acute alteration of mental status. Septic shock was defined as sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction. Patients receiving inotropic or vasopressor agents may no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction, yet they would still be considered to have septic shock [34]. Since 1994, PMX-DHP therapy has been approved as a blood purification treatment in Japan and is covered by Japanese National Health Insurance [35]. From January 2009 to December 2012, 7 of 182 (3.8 %) patients with post-esophagectomy who were diagnosed with severe sepsis or septic shock underwent PMX-DHP therapy in addition to conventional therapy as a routine protocol at our institution. These patients were compared to 8 of 206 (3.9 %) patients with post-esophagectomy who only received conventional therapy from January 2001 to December 2008. Conventional therapy refers to the treatment for post-esophagectomy sepsis and includes abscess drainage, antibiotics, transfusion, vasopressors (including catecholamines), mechanical ventilation, glycemic control, renal replacement therapy, etc. Among the seven patients in the PMX-DHP therapy group, four had pneumonia, two had anastomotic leakage, and one had reconstructed colon necrosis. Among the eight patients in the conventional therapy group (i.e., the control therapy group), three had pneumonia, three had anastomotic leakage, and two had gastric tube necrosis.

Pneumonia was diagnosed using chest X-ray and chest computed tomography (CT), clinical presentation, sputum culture, and clinical examination. Anastomotic leakage was diagnosed through contrast study of the anastomosis. Gastric tube necrosis and reconstructed colon necrosis were diagnosed by clinical examination, CT, and esophagogastroduodenoscopy.

All patients were male and aged from 63 to 75 years (mean 69.5 years). Blood and sputum cultures were performed to identify causative pathogens. Endotoxin levels were also measured in the PMX-DHP therapy group.

We retrospectively investigated the improvement in general status, which was primarily determined by the Sequential Organ Failure Assessment (SOFA) score [36, 37]. In the present study, the Glasgow Coma Scale was excluded from the SOFA score because several patients required sedation for mechanical ventilation.

PMX-DHP therapy

When patients with sepsis met the inclusion criteria, PMX-DHP (PMX; Toray Medical, Tokyo, Japan) therapy was administered using a polystyrene fiber column to which polymyxin B was covalently bound at a weight ratio of 0.5 %. Strong binding of polymyxin B to the column was previously confirmed. Access for PMX-DHP therapy was obtained via a double-lumen catheter inserted into the femoral vein. PMX-DHP therapy was administered for 2–5 h at a flow rate of 100–120 mL/min. Nafamostat mesilate and/or heparin sodium was used as anticoagulants.

Other therapeutic methods

Other therapeutic methods for patients with severe sepsis and septic shock post-esophagectomy included a crystalloid and/or colloid fluid solution administered to maintain a systolic blood pressure of at least 90 mmHg. When adequate fluid could not restore the blood pressure, therapy with vasopressor agents was initiated. Intravenous broad-spectrum antibiotic therapy was initiated after appropriate cultures were obtained. Source control measures (drainage

of an abscess or surgical procedure) were instituted as soon as possible after initial resuscitation. In cases with respiratory failure, mechanical ventilation was performed with intratracheal intubation. In cases with renal failure, renal replacement therapy was performed. All cases were treated in the ICU.

Statistical analysis

Data were analyzed using SPSS for Windows ver. 18.0 (SPSS, Chicago, IL, USA). All values are presented as mean ± SD, medians (ranges), or numbers (percentages). Associations between categorical variables were assessed using Pearson's Chi-square test or Fisher's exact test. Continuous variables were compared using the unpaired Student's t test or Mann–Whitney U test. $P < 0.05$ was considered to indicate statistical significance.

Results

Baseline demographics

Demographic characteristics of patients are summarized in Table 1. Data were obtained at the time of sepsis diagnosis. There were no significant differences between the conventional and PMX-DHP therapy groups with regard to any parameter.

Bacteriology

Microorganisms were isolated from all patients (Table 1). The most common causative organisms were methicillin-resistant *Staphylococcus aureus* ($n = 6$, 40 %) and *Pseudomonas aeruginosa* ($n = 5$, 33 %). Gram-negative bacilli were found in eight patients (53 %). *Candida* species were not found in any patient. There were no differences in the incidence of causative organisms between the two groups.

Surgical data

Details of the surgical data are shown in Table 2. No significant differences were found between the two groups with regard to any parameter.

In-hospital outcomes

In-hospital outcomes are summarized in Table 3. The 30- and 90-day mortality rates for the PMX-DHP therapy group were zero, whereas those for the conventional therapy group were 25 % (one, pneumonia; and one, relapse of sepsis) and 37.5 % (two, pneumonia; and one, relapse of sepsis), respectively. Length of stay in the ICU for patients in the PMX-DHP and conventional therapy groups was 14.0 and 25.5 days, respectively ($P = 0.040$).

Table 1 Demographic characteristics of patients

Characteristics	Conventional therapy group ($n = 8$)	PMX-DHP therapy group ($n = 7$)	P
Age (years)	65.1 ± 4.2	68.4 ± 5.5	0.21
Male/female	7/1	7/0	0.46
ASA-PS	2.1 ± 0.4	2.1 ± 0.7	0.95
Pathology (SCC/adenocarcinoma)	6/2	7/0	1.0
Leukocyte count ($\times 10^3$/mm^3)	15.0 ± 10.9	8.2 ± 3.2	0.13
Platelet count ($\times 10^3$/mm^3)	215.9 ± 131.1	118.2 ± 78.1	0.11
Total bilirubin (mg/dL)	2.1 ± 0.7	2.0 ± 1.0	0.94
Creatinine (mg/dL)	1.5 ± 1.0	1.8 ± 1.6	0.70
Albumin (g/dL)	2.8 ± 0.6	2.4 ± 0.6	0.26
CRP (mg/dL)	20.2 ± 8.1	14.0 ± 3.7	0.09
PaO_2/FiO_2 ratio	156 ± 66.4	162 ± 88.8	0.90
SOFA score	8.1 ± 1.0	9.1 ± 0.69	0.09
Cause of sepsis			0.61
Anastomotic leakage	3	2	
Pneumonia	3	4	
Gastric tube necrosis	2	0	
Reconstructed colon necrosis	0	1	
Reoperation for sepsis therapy	3 (38 %)	3 (43 %)	0.60
Drainage surgery for anastomotic leakage	1	1	
Partial gastric resection	2	0	
Partial colonic resection	0	1	
Tracheal repair surgery	0	1	
Enteral nutrition	5 (63 %)	5 (71 %)	1.0
Bacteriology			0.44
MRSA	5	1	
P. aeruginosa	3	2	
Others	4	5	

ASA-PS American Society of Anesthesiologists physical status, *CRP* C-reactive protein, *SCC* squamous cell carcinoma, *SOFA* Sequential Organ Failure Assessment, *MRSA* methicillin-resistant *Staphylococcus aureus*

Table 2 Surgical data

Parameter	Conventional therapy group ($n = 8$)	PMX-DHP therapy group ($n = 7$)	P
Operation method			
Open	4 (50 %)	6 (86 %)	0.28
Laparoscopy	4 (50 %)	1 (14 %)	
Lymphadenectomy			1.0
Two-field	4 (50 %)	3 (43 %)	
Three-field	4 (50 %)	4 (57 %)	
Reconstruction			
Route			
Presternal	4 (50 %)	3 (43 %)	1.0
Posterior mediastinal	4 (50 %)	4 (57 %)	
Organ			0.20
Gastric tube	8 (100 %)	5 (71 %)	
Reconstructed with colon	0 (0 %)	2 (29 %)	
Operation time (min)	431.9 ± 75.8	537.3 ± 131.6	0.08
Blood loss (mL)	391.4 ± 297.0	276.7 ± 120.0	0.34
Transfusion during surgery			
Red cell concentrates (mL)	140 ± 259.2	240 ± 440.6	0.60
Curativity (R0/R1/R2)	5/2/1	6/1/0	0.51

Detailed characteristics of seven patients in the PMX-DHP therapy group

Table 4 shows a summary of the clinical characteristics of patients in the PMX-DHP therapy group. Six patients had septic shock and one had severe sepsis. Plasma endotoxins were not detected in any of the patients belonging to this group.

Comparison of the SOFA score and P/F ratio

Details of the comparison data of the SOFA score and P/F ratio are shown in Table 5. We compared the SOFA score and P/F ratio between the time of diagnosis of severe sepsis or septic shock (A) and 12–24 h after the time of diagnosis (B). The total SOFA score was significantly lower ($P = 0.0027$) in the post-PMX-DHP therapy group; in particular, the respiratory system score was significantly lower ($P = 0.025$) in the post-PMX-DHP therapy group. In addition, the actual P/F ratio was significantly higher ($P = 0.0087$) in the post-PMX-DHP therapy group. We compared the variations in the SOFA score and P/F ratio between the conventional and PMX-DHP therapy groups. The variations in the improvement in the total SOFA score, respiratory system score, and P/F ratio were significantly higher ($P = 0.019$, $P = 0.0063$, and $P = 0.0015$, respectively) in the PMX-DHP therapy group. We compared the SOFA score and P/F ratio between the conventional and PMX-DHP therapy groups at the time of discharge from the ICU. The respiratory system SOFA score was significantly lower ($P = 0.0062$), and the actual P/F ratio was significantly higher ($P = 0.042$) in the PMX-DHP therapy group. No side effects of PMX-DHP therapy were observed in any of the patients.

Discussion

In the present study, PMX-DHP therapy decreased the length of stay in the ICU and improved respiratory and general conditions in patients with post-esophagectomy sepsis. To the best of our knowledge, this is the first report to demonstrate the clinical utility of PMX-DHP therapy in patients with post-esophagectomy sepsis. PMX-DHP therapy may be efficacious for post-esophagectomy complications, although some reports have indicated its utilities on lower gastrointestinal tract perforations [38–40]. Our study indicates that PMX-DHP therapy may be useful for management of gram-negative and/or gram-positive bacterial sepsis and endotoxin-negative sepsis.

In comparison with other post-esophagectomy complications, sepsis and septic shock remain important causes of morbidity and mortality. In spite of various treatments, sepsis leads to multiorgan dysfunction. The Surviving Sepsis Campaign recommended the following international guidelines for the management of severe sepsis and septic shock: (1) early goal-directed resuscitation of affected patients during the first 6 h after diagnosis; (2) lung-protective ventilation; (3) after obtaining cultures, administration of broad-spectrum antibiotics; and (4) other treatment measures, including correction of anemia and glycemic control (targeting an upper blood glucose level of $\leq$180 mg/dL) [41]. In spite of these aggressive treatment measures, rates of sepsis-induced multiorgan dysfunction and mortality due to sepsis and septic shock remain high. Cruz et al. [42] recently reported the results of the Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis (EUPHAS) study. This study analyzed whether PMX-DHP therapy improved the mean arterial pressure and resulted in fewer requirements for vasopressors in patients with septic shock presumed to be caused by abdominal infections. In this preliminary study, PMX-DHP therapy improved hemodynamics, ameliorated organ dysfunction, and decreased 28-day mortality. Two other randomized controlled trials, the Effects of Hemoperfusion With a Polymyxin B Membrane in Peritonitis With Septic Shock (ABDO-MIX) and Evaluating the Use of Polymyxin B

Hemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxemia and Septic Shock (EUPHRATES), the primary endpoints of which were 28-day mortality, were started in Europe and the US at the end of 2010.

Recent studies have also reported that PMX-DHP therapy decreases blood levels of neutrophil elastase [30], tumor necrosis factor-α [43], and matrix metalloproteinase-9, which enhances vascular permeability [33], as well as decreases the intrapulmonary shunt ratio [44]. Other studies have also reported that PMX-DHP therapy decreases the levels of interleukin (IL)-6, IL-10, IL-18, plasminogen activator inhibitor-1, platelet factor-4, β-thromboglobulin, soluble P selectin, and endogenous cannabinoid [28, 45, 46]. Sakamoto et al. reported that systolic blood pressure significantly increased whereas high mobility group box 1 (HMGB1) protein levels decreased after PMX-DHP therapy; further, they showed that the circulation dynamics of septic shock patients could be improved by decreasing HMGB1 levels [47, 48]. We previously reported the correlation between postoperative serum HMGB1 levels and complications [49]. PMX-DHP therapy may be able to interrupt the inflammatory cascade, providing time for antibiotic, surgical, and supportive therapies to become effective. PMX-DHP therapy is also therapeutic by itself. It eliminates several agents, besides etiological agents, resulting in the amelioration of shock. Some investigators recently reported that PMX-DHP therapy ameliorates the state of shock not only in patients with gram-negative

Table 3 In-hospital outcome

Outcome	Control therapy group ($n = 8$)	PMX-DHP therapy group ($n = 7$)	*P*
30-day mortality	2 (25 %)	0 (0 %)	0.47
90-day mortality (including 30-day mortality)	3 (37.5 %)	0 (0 %)	0.20
Clinical cure for sepsis	4 (50 %)	6 (85.7 %)	0.28
Length of stay in the ICU (days)	25.5 (11–66)	14 (9–18)	**0.040**

Bold value indicates a statistically significant difference with a *P*-value less than 0.05

Table 4 A summary of the clinical characteristics of the PMX-DHP therapy group

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (years)	75	75	72	65	67	63	62
Sex	M	M	M	M	M	M	M
ASA-PS	3	2	2	2	3	2	1
Pathology	SCC	SCC	SCC	SCC	SCC	SCC	SCC
NAT	None	NAC	NAC	NAC	NAC	None	NAC
Operation method	Open	LAP	Open	Open	Open	Open	Open
Lymphadenectomy	2F	3F	2F	2F	3F	3F	3F
Reconstruction							
Route	Po	Po	Pr	Po	Pr	Pr	Po
Organ	GT	GT	GT	GT	Colon	Colon	GT
Complication	AL	Pneumonia	Pneumonia	Pneumonia	AL	RCN	Pneumonia
State of sepsis	Shock	Shock	Shock	Shock	Shock	Severe	Shock
Causative pathogen	*P. aeruginosa*	MRSA	*K. pneumoniae* *E. cloacae*	*S. maltophilia*	*E. cloacae*	*E. coli*	*P. aeruginosa*
Source of pathogen	Mediastinal abscess	Sputum	Sputum	Sputum	Abdominal abscess	Blood	Sputum
Endotoxin	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Day of PMX-DHP	13 POD	9 POD	6 POD	9 POD	15 POD	7 POD	5 POD
Time lag	3.3 h	5.0 h	3.0 h	3.3 h	1.5 h	6.5 h	0.8 h
Duration of PMX-DHP therapy	2 h 40 m	2 h 20 m	3 h 3 m	4 h 35 m	2 h 5 m	2 h 0 m	2 h 0 m
Outcome	RFS	Cancer death	Cancer death	RFS	Death by liver failure	RFS	RFS

M male, *NAT* neoadjuvant therapy, *NAC* neoadjuvant chemotherapy, *LAP* laparoscopy, *2F* two-field, *3F* three-field, *Po* Posterior mediastinal, *Pr* Presternal, *GT* gastric tube, *AL* anastomotic leakage, *RCN* reconstructed colon necrosis, *Time lag* the time lag between the time of sepsis diagnosis and initiation of PMX-DHP therapy, *h* hour, *MRSA* methicillin-resistant *Staphylococcus aureus*, *m* minute, *RFS* recurrence-free survival

Table 5 Comparison of the SOFA score and P/F ratio

Measurement time	Group	The time of diagnosis of sepsis (A)		After 12–24 h (B)	*P* (A vs. B)	The variation of (A) and (B)	*P* (PMX vs. CT)	The time of discharge of ICU	*P* (PMX vs. CT)
Respiratory system	PMX	2.9 ± 0.90	PMX-DHP	1.6 ± 0.98	**0.025**	−1.3 ± 0.49	**0.0063**	1.3 ± 1.1	**0.0062**
	CT	3.0 ± 0.76		2.8 ± 0.46	0.35	−0.25 ± 0.71		3.0 ± 0.93	
P/F ratio	PMX	162 ± 88.8	PMX-DHP	306 ± 83.5	**0.0087**	144 ± 44.6	**0.0015**	371 ± 196	**0.042**
	CT	156 ± 66.4		175 ± 50.7	0.50	18.2 ± 71.7		175 ± 96.2	
Coagulation	PMX	1.4 ± 1.3	PMX-DHP	1.0 ± 1.3	0.54	−0.43 ± 0.53	0.15	0.86 ± 0.69	0.46
	CT	0.50 ± 0.76		0.50 ± 1.1	1.0	0.0 ± 0.53		1.4 ± 1.7	
Liver	PMX	1.4 ± 0.79	PMX-DHP	1.1 ± 0.90	0.54	−0.29 ± 0.49	0.19	1.0 ± 1.3	0.24
	CT	1.4 ± 0.74		1.5 ± 0.76	0.60	0.13 ± 0.64		1.9 ± 1.5	
Cardiovascular system	PMX	2.4 ± 1.4	PMX-DHP	1.4 ± 1.8	0.27	−1.0 ± 1.0	0.11	0.57 ± 1.5	0.22
	CT	2.5 ± 0.53		2.3 ± 0.46	0.35	−0.25 ± 0.71		1.8 ± 2.0	
Renal system	PMX	1.0 ± 1.4	PMX-DHP	0.71 ± 1.4	0.68	−0.29 ± 0.49	0.082	0.86 ± 1.6	0.87
	CT	0.75 ± 1.0		0.88 ± 1.2	0.35	0.13 ± 0.35		0.75 ± 0.89	
Total score	PMX	9.1 ± 0.69	PMX-DHP	5.9 ± 1.9	**0.0027**	−3.3 ± 2.1	**0.019**	4.6 ± 2.9	0.11
	CT	8.1 ± 1.4		7.9 ± 2.4	0.77	−0.25 ± 2.3		8.8 ± 6.1	

Negative values of the SOFA score for the variation of (A) and (B) indicate improvement in organ function, and positive values indicate worsening. Positive values of the P/F ratio for the variation of (A) and (B) indicate improvement in respiratory function, and negative values indicate worsening

Bold values indicate a statistically significant difference with a *P*-value less than 0.05

SOFA Sequential Organ Failure Assessment, *PMX-DHP* polymyxin B-direct hemoperfusion, *CT* conventional therapy, *P/F ratio* PaO_2/FiO_2 ratio

infections but also in those without such infections [50, 51]. Several studies have shown that PMX-DHP therapy results in improvement in pulmonary oxygenation patients with septic shock, a condition associated with decreased adhesion molecules [52]. One study reported significant negative correlations between the P/F ratio and IL-8 and neutrophil elastase levels in patients with septic shock [24]. Another study reported that PMX decreased the levels of metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in patients with ARDS. The improved P/F ratio conferred by PMX hemoperfusion may therefore be attributable to decreases in the levels of adhesion molecules, IL-8, neutrophil elastase, metalloproteinase-9, or tissue inhibitor of metalloproteinase-1 [52].

There were several limitations to this study. First, the number of subjects was less. Second, because all patients undergoing PMX-DHP therapy were concurrently treated with other therapies, the observed improvement in the general condition may not be exclusively attributable to PMX-DHP therapy. Thus, further studies are required. We need to perform a prospective multicenter trial in a targeted population of patients with each complication (i.e., pulmonary complications, anastomotic leakage, and so on) who have post-esophagectomy sepsis.

In summary, we found a favorable clinical response to PMX-DHP therapy among patients with post-esophagectomy sepsis. Although the sample size was small, we showed the potential utility of PMX hemoperfusion for post-esophagectomy sepsis. Further studies should elucidate the efficacy of early use of PMX-DHP therapy for post-esophagectomy sepsis.

Ethical Statement This study was approved by the Ethics Committee of Keio University School of Medicine and was in accordance with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

Conflict of interest There are no financial or other relations that could lead to a conflict of interest.

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