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Why measure endotoxin in Septic Shock Patients

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Introduction:
Aim of the study:to evaluate the clinical utility of endotoxin activity(EAA) measurement in critically-ill Septic Shock (SS)Patients(Pts).
Methods:
From January 2007 to August 2007 in a 8 bed general ICU, we performed a prospective analysis of EAA level on 29 critically-ill Pts within 24hr of SS diagnosis(CDC criteria).EAA level was assessed by a new and rapid assay based on neutrophil-dependent chemioluminescence. EAA level (defined as low,intermediate and high respectively for values of <0.40, 0.40-0.60, and ≥0.6) was then correlated with severity of illness and ICU mortality.
Results:
The clinical profile of SS Pts is shown in table1.EAA level was low in a minority of SS-Pts (13%), an intermediate and high EAA level were evidenced in 31% and 56%of SS Pts respectively (table2).Our results seem to evidence a good correlation between EAA levels and severity of illness (table 2). EAA level seems to correlate with ICU mortality wich was 0% in low EAA Pts,17 and 37% in intermediate and high EAAPts
Conclusions:
Although our sample is too small to reach statistically significance EAA level could be a good marker of severity in SS Pts. High level of EAA seems to correlate with worse prognosis in SS Pts.

References:

Table 1:
Age(yrs) 58,6 ±16,4
PCR(mg/dl) 27 ± 10
VAM/CRRT 90%/22,5%
SOFA/SAPSII 12,3±3/47±9
GRam+/- 24%/17%
Clinical profile of SS Pts

Table 2:

	EA<0,4	0,4<EA<0,6	EA>0,6
MAPmmHg	86.8±4.7	80.5±5.8	79.3±17.1
NEu/Kg/min	0.36±0.21	0.43±0.36	0.68±0.53
Lac mmol	3.0±1.5	3.9±3.7	6.4±5.8
SOFA	9.7±5	10.1±3.	12.6±3.8
CI l/min/m	3.78±1.26	4.16±1.14	3.64±2.10

EAA level and severity of illness

Почему следует измерять активность эндотоксина у больных септическим шоком.

Введение:
Цель исследования: оценить клиническую целесообразность анализа активности эндотоксина (АЭ) у критических пациентов с септическим шоком (СШ).

Методы:
С января 2007 по август 2007 года в 8-местном ОИТ общей практики, мы провели проспективный анализ уровней АЭ у 29 критических больных с суточным диагнозом СШ (китерии CDC). Для оценки уровня АЭ был использован новый и быстрый анализ, основанный на нейтрофил-зависимой хемолюминисценции. Уровень АЭ (определяется как низкий, средний и высокий, соответственно, для значения <0.40, 0.40-0.60, и ≥ 0,6) был связан с тяжестью заболевания и смертностью с ОИТ.

Результаты:
Клинические профили пациентов с СШ показаны в Таблице 1. Уровень АЭ был низким у меньшинства пациентов с СШ (13%), средний и высокий уровни АЭ определялись у 31% и 56% пациентов с СШ соответственно (Таблица 2). Наши результаты доказывают хорошую корреляцию между уровнями АЭ и тяжестью заболевания (Таблица 2). Уровень АЭ заметно коррелирует со смертностью в ОИТ, которая составляет 0% у пациентов с низким уровнем АЭ, 17 и 37% у пациентов со средним и высоких уровнем АЭ.

Выводы:
Хотя наша выборка слишком мала, чтобы достичь уровня статистической значимости, уровень АЭ может быть хорошим показателем степени тяжести пациентов с СШ. Высокий уровень АЭ заметно коррелирует с худшим прогнозом у пациентов с СШ.

Список литературы:

Таблица 1, Клинические профили пациентов с СШ:

Возраст (годы)	58,6 ±16,4
Креатинин плазмы (мг/дл)	27 ± 10
ИВЛ/CRRT	90%/22,5%
Тяж. ПОН/Тяж. состояния пациентов в группах	12,3±3/47±9
Грам+/-	24%/17%

Table 2, Уровень АЭ и тяжесть заболевания:

	АЭ<0,4	0,4<ЕА<0,6	ЕА>0,6
Ср. АД mmHg	86.8±4.7	80.5±5.8	79.3±17.1
Инф. адреналина Ед/кг/мин	0.36±0.21	0.43±0.36	0.68±0.53
Лактат ммоль	3.0±1.5	3.9±3.7	6.4±5.8
Тяж. ПОН	9.7±5	10.1±3.	12.6±3.8
СИ л/мин/м2	3.78±1.26	4.16±1.14	3.64±2.10

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Polymyxin B hemoperfusion in high endotoxin activity level Septic Shock Patients.

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Introduction:
Aim of the study: to evaluate the clinical impact of Polymyxin-B Hemoperfusion (HP-PMX) as adjuvant therapy versus conventional treatment in Septic Shock (SS) Patients (Pts) with high endotoxemia.
Methods:
a retrospective analysis on the clinical profile and evolution related to treatment strategy of SS Pts with high endotoxin activity (EA) level (>0,6 units) attended in our ICU from January to August 2007. All Pts (n=16) were treated with standard therapy (ST) according to SSC. According to our ICU practice, adjuvant therapy with HPPMX (twice, 2hr/session with interval of 24hr) was performed only in SS Pts with known or presumed Graminfection, worsening of haemodynamic instability in the next 6 hours of diagnosis and ≥3 organ failures (PMX group, n=8). The clinical profile was evaluated in the two groups (ST vs PMX group) at T0 (SS diagnosis, start of HP-PMX) and at T1 (at 48hr). T student test for paired values was used for statistical purpose ($p < .05 = *$).
Results:
at T0 the clinical profile of the two groups of high EA level SS Pts was similar (EA level, age, SOFA, MAP, NEP, lactates, PaO2/FiO2, CRRT, used of APC). Otherwise the PMX group showed a significant improvement of clinical conditions compared to ST group at T1 (Table 1). ICU LOS was significantly longer in PMX group vs ST group (21.5±21,3vs53.6±67days*). Further PMX-HP resulted in a reduction of ICU mortality when compared to standard therapy in high EA level Septic Shock Pts probably due to endotoxin removal (45vs16%, NS due to small sample size).
Conclusions:
we can question if EA level could be a usefull guide to early institution of specific anti-LPS treatments.
References:

Table 1 :

	T0	T1	p value
NEP ST	0.58	0.33	NS
NEP PMX	0.85	0.28	$p < .05$
SOFA ST	11.5	11.1	NS
SOFA PMX	14.15	12.17	$p < .05$
LAC ST	5.41	4.71	NS
LAC PMX	7.94	5.35	$p < .05$

Evolution of high EA level SS Pts

Гемоперфузия с Полимиксином Б при высоком уровне активности эндотоксина у больных с септическим шоком.

Введение:
Цель исследования: оценить клиническое воздействие гемоперфузии с Полимиксином Б (ПМ-ГП) в качестве адъювантной терапии по сравнению с обычным лечением септический шока (СШ) у больных (Б.) с высоким эндотоксикозом.

Методы:
В нашем ОИТ с января по август 2007 года проводился ретроспективный анализ клинического профиля и связанные с развитием болезни стратегии лечения СШ у П. с высокими уровнями активности эндотоксина (АЭ) (> 0,6 единицы). Всех П. (N = 16) лечили стандартной терапией (СТ) в соответствии с рекомендациями Компании за Выживание Больных Сепсисом.
В соответствии с практикой, принятой в нашем ОИТ, терапия ПМ-ГП (в два раза, по 2 часа на процедуру с интервалом 24 часа) была выполнена только у П. с СШ с известной или предполагаемой грамотрицательной инфекцией, диагностированным ухудшением гемодинамических показателей в ближайшие 6 часов и отказами ≥ 3 органовз (ПМ группа, N = 8). Клинический профиль был оценена в двух группах (СТ vs ПМ группа) при Т0 (диагноз СШ, начало ПМ-ГП) и Т1 (на 48 часу). Для статистических целей был использован критерий Т Стьюдента для парных значений (P <.05 =*).
Результаты:
при Т0 клинические профили двух групп пациентов с СШ и высоким уровнем АЭ были похожими (АЭ, возраст, тяжесть ПОН, САД, НА, лактат, PaO2/FiO2, CRRT, уровня АПС). Напротив, группа ПМ показала значительное улучшение клинических показателей по сравнению с группой СТ на Т1 (табл. 1). Продолжительность нахождения в ОИТ была значительно дольше в группе ПМ против СТ группы (21,5 ± 21,3 vs 53.6 ± 67 дня*). Дальнейшее проведение ПМ-ГП привело к снижению смертности в ОИТ по сравнению со стандартной терапией при высоком уровне АЭ у пациентов с СШ, вероятно, из-за удаления эндотоксина (45 против 16%, недостоверно из-за небольшого размера выборки).
Выводы:
остаётся вопрос, может ли руководствоваться уровнем АЭ, как полезным критерием для раннего назначения конкретной анти-ЛПС терапии.
Список литературы:

Таблица 1

	Т0	Т1	р критерий
НА, СТ	0.58	0.33	незнач.
НА, ПМ	0.85	0.28	p < .05
Тяж. ПОН, СТ	11.5	11.1	незнач.
Тяж. ПОН, ПМ	14.15	12.17	p < .05
Лактат, СТ	5.41	4.71	незнач.
Лактат, ПМ	7.94	5.35	p < .05

Динамика показателей у пациентов с СШ и высоким уровнем АЭ

Intensive Care Med. 1998 Dec;24(12):1272-6.

Changes in plasma erythropoietin and interleukin-6 concentrations in patients with septic shock after hemoperfusion with polymyxin B-immobilized fiber.

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OBJECTIVE: To find out whether polymyxin B-immobilized fiber (PMX-F) treatment affects the clinical parameters and plasma concentrations of erythropoietin (EPO) and interleukin (IL)-6.
DESIGN: A prospective case series study.
SETTING: Intensive care unit of the Department of Internal Medicine, Misato Junshin Hospital, Saitama, and Koto Hospital, Tokyo, Japan.
PATIENTS: 17 consecutive patients (10 men, 7 women; mean age 54.6 years) with clinically defined septic shock and 20 healthy volunteers (12 men, 8 women; mean age 52.2 years).
MAIN RESULTS: Of the 17 patients with septic shock, 9 (53 %) survived. The systolic blood pressure increased significantly from 78+/-6 to 106+/-8 mm Hg 2 h after PMX-F treatment in patients with septic shock. Plasma endotoxin levels decreased significantly after treatment, from 40+/-6 to 12+/-4 pg/ml. The pretreatment plasma concentrations of EPO and IL-6 were significantly higher in the 8 nonsurviving patients with septic shock (EPO: 400+/-36 mIU/ml; IL-6: 6260+/-1180 pg/ml) than in the 9 surviving patients (EPO: 120+/-22 mIU/ml; IL-6: 680+/-138 pg/ml) and the 20 control subjects (EPO, 12+/-6 mIU/ml; IL-6, 8+/-2 pg/ml). Plasma concentrations of EPO and IL-6 in patients with septic shock decreased significantly after PMX-F treatment (EPO, nonsurviving: 320+/-28 mIU/ml, $p < 0.05$; survivors: 26+/-8 mIU/ ml, $p < 0.001$; IL-6, nonsurviving: 3860+/-840 pg/ml, $p < 0.01$; survivors: 84+/-20 pg/ml, $p < 0.001$).
CONCLUSIONS: Plasma concentrations of EPO and IL-6 may be prognostic indicators in patients with septic shock: PMX-F treatment may be effective in reducing the plasma concentrations of EPO and IL-6 in patients with septic shock.

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Oxygen metabolism as an indicator in criteria for hemoperfusion using a polymyxin-B immobilized column introduction

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Introduction It has been reported that hemoperfusion with a column of polymyxin B immobilized on fibers (PMX-DHP) ameliorates hyperdynamic circulation in septic shock and improves survival rate. However, a variety of criteria for the introduction of PMX-DHP in sepsis patients are used by a number of facilities, standard criteria have yet to be established. We introduced PMX- DHP using oxygen metabolism as an indicator, and evaluated the effectiveness. Subjects and methods Subjects consisted of 24 sepsis patients (19 men and five women; mean age 60 ± 15.4 years) who had undergone PMX-DHP between January 2003 and October 2004. A thermodilution catheter was inserted into all patients. Mixed venous oxygen saturation (SvO2), oxygen delivery index (DO2I), oxygen consumption index (VO2I), and oxygen extraction ratio (O2ER) were used as indicators of systemic oxygen metabolism, and the PCO2 gap (gastric submucosal carbon dioxide partial pressure minus the partial pressure of carbon dioxide in arterial blood) measured by gastric air tonometry was used as the indicator of tissue oxygen metabolism. These parameters were measured before and 24, 48, 72, and 120 hours after PMX-DHP introduction. The severity of infection was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) score. Results Life expectancy: 18 patients survived; six died. APACHE scores of survivors and non-survivors were 22 ± 4.0 and 24 ± 3.5, respectively. There was no significant difference. In the survivors SvO2, DO2I, VO2I, and O2ER had shifted to the normal range prior to treatment. Pretreatment, the PCO2 gap was 17 ± 3.6 mmHg in these patients, who presented markedly dysfunctional tissue oxygen metabolism. However, this decreased over time, and at 120 hours after treatment the PCO2 gap had decreased significantly, improving to values in the normal range. On the other hand, the non-survivors also presented high PCO2 gap levels before treatment, similar to the survivors. Although DO2I was within the normal range, VO2I and O2ER were lower than normal. Conclusion Although dysfunctional tissue oxygen metabolism occurred in both the survivors and non-survivors, non-survivors also presented dysfunctional systemic

oxygen intake. These results suggest that early-stage introduction of PMX-DHP is desirable, when systemic oxygen metabolism is stable.

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Early introduction of hemoperfusion with an immobilized polymyxin B fiber column eliminates humoral mediators and improves pulmonary oxygenation

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Introduction We previously reported that early introduction of hemoperfusion with an immobilized polymyxin B fiber column (PMX-DHP) improved life expectancy. This time, we report that early introduction of PMX-DHP eliminates humoral mediators and improves pulmonary oxygenation.
Subjects and methods Thirty-six sepsis patients were the subjects, consisting of 21 men and 15 women aged 62 ± 18.5 years. A thermodilution catheter was inserted in each patient, and the mixed venous oxygen saturation, oxygen delivery index, oxygen consumption index, and oxygen extraction ratio were measured. After it was confirmed that systemic oxygen metabolism was not impaired, PMX-DHP was started. Patients with uncontrolled infection were excluded from the study. The Acute Physiology and Chronic Health Evaluation (APACHE II) score was used as the index of severity, and survival of the patients was assessed after 1 month. The humoral mediators measured were IL-8 as a chemokine, plasminogen activator inhibitor-I (PAI-1) as an index of vascular endothelial cell activation, and polymorphonuclear neutrophil elastase (PMN-E) as an index of neutrophil activation. These mediators were measured before the start of PMX-DHP, and at 24, 48, and 78 hours after the start. The PaO2/FiO2 (P/F) ratio was used as an index of pulmonary oxygenation; it was measured before the start of PMX-DHP, and at 24, 48, 72, 92, and 120 hours after the start.
Results Due to the early introduction of PMX-DHP with oxygen metabolism as the index, all the patients remained alive after 1 month. Before the start, the APACHE II score was 24±2.0. Before treatment, the IL-8 level was 54±15.8 pg/ml, but it decreased significantly from 48hours onwards. PAI-1 was 133±28.1 before treatment, but decreased significantly from 48 hours onwards. Similarly, PMN-E was also a high 418±72.1 before treatment, but improved significantly from 48hours onwards. The P/F ratio was 228±68 before treatment, but improved significantly from 96 hours onwards.
Conclusion The mechanism of action of PMX-DHP is still not fully understood, but the following findings were clarified from our investigation. (1) Early introduction of PMX-DHP improves life expectancy. (2) It is probable that changes of humoral mediators inhibit vascular endothelial cell activation, neutrophil activation, and chemokine activation. (3) It is probable that pulmonary oxygenation is improved due to elimination of humoral mediators.

G Ital Nefrol. 2006 May-Jun;23 Suppl 36:S94-102.

[Polymyxin-B direct hemoperfusion (PMX-DHP) in gram negative sepsis].

[Article in Italian]

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Severe sepsis and septic shock have a mortality rate that may range between 28 and 50%. It is estimated that approximately 200,000 patients die per annum in the USA as a consequence of sepsis. The reduction of plasma endotoxin levels to achieve a favourable outcome for septic patients has been previously demonstrated but the effectiveness of treatments targeting single inflammatory mediators during established sepsis has been disappointing. Furthermore,some clinical study clinically showed valuable reduction in cytokine levels by hemofiltration alone. The prompt removal of endotoxins could be an effective way to reduce the immunological activation and the amount of NO produced by endotoxin-activated inducible NO-synthase in many tissues and cells. The polymyxin B cartridge is an extracorporeal hemoperfusion device (PMX-DHP) known to remove circulating endotoxins. Open-label clinical trials testing PMX-DHP have demonstrated its safety in the septic shock treatment while the overall survival rate significantly improved in comparison with the control groups. The purpose of this study was to investigate the effects of PMX-DHP on redox status, inflammatory cytokine profile, monocytes and PMN leukocyte activation in Gram-negative sepsis. Prospective study: six patients, 2 males and 4 females 60.5+/-24.5 years old, in ICU for severe Gram-negative sepsis (emergency surgery for intra abdominal infection). Two PMX-DHP

runs, at T0 and T1; 2 hours each; the first within 24 hours from sepsis diagnosis or 12 hours after emergency surgery, the first PMX-DHP at T0, the second after 24 hours.; APACHE II score at T0: 20.1+/-3.7; SOFA score 14.2+/-2.5; organ failure: 3+/-1.5; norepinephrine(Ne) in 1 patient; Ne + dopamine (DA) in 4 patients; DA in 1 patient only. Mean dosage: Ne 0.24 mcg/kg/min; DA 8.9 mcg/kg/min. Four patients in CRRT (continuous veno-venous hemofiltration, AN69 hemofilter) for the entire length of the study. QB 100+/-10 ml/min. Pre and post PMX-DHP, plasma endotoxins as well as anti-IL 1-beta, IL2, IL4, IL5, IL6, IL8, IL10, TNF-alpha, GM-CSF, IFN-gamma levels were measured. Expression of CD64 on monocytes and PMN leukocytes and I -2r CD25 on CD4+ T cells by flow cytometry. Total and reduced plasma cysteine, homocysteine, glutathione (GSH); plasma glutathione peroxidase (GSH-Px) and reductase (GSH-Rx); erythrocyte GSH (eGSH), eGSH-Px and eGSH-Rx; NADP and NADPH and their ratio assessed pre and post PMX-DHP, all compared with 15 age and gender-matched healthy subjects for complete REDOX characterization. Results: We observed a significant reduction of endotoxin levels post PMX-DHP; CD64 monocytes and PMN leukocytes overexpression returned to normal; pro-inflammatory cytokines Il6, Il 10 and TNF-alpha were significantly reduced. We detected no differences in plasma levels of anti-IL 1-beta, IL2, IL4, IL5, IL8, GM-CSF, IFN-gamma pre versus post PMX-DHP. SOFA score from 14.2+/-2.5 to 8.9+/-2.1 post PMX-DHP runs. Four out of six patients survived and were discharged; mortality was 33% versus the anticipated 51%. Conclusion: PMX-DHP reduces circulating endotoxins, down-activates monocytes and PMN leukocytes, reduces pro-Inflammatory cytokines and corrects the redox environment imbalance preventing oxidative damage to endothelial cells and the metabolic and functional microvascular derangements that usually lead to multi-organ failure and septic shock.

Ther Apher Dial. 2006 Feb;10(1):7-11.

The effect of continuous veno-venous hemofiltration or direct hemoperfusion with polymyxin B-immobilized fiber on neutrophil respiratory oxidative burst in patients with sepsis and septic shock.

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Neutrophil activates and injures tissues and organs during sepsis or septic shock. Blood purification therapies such as continuous veno-venous hemofiltration (CVVH) and direct hemoperfusion with polymyxin-immobilized fiber (PMX-DHP) have been used for the treatment of sepsis and septic shock, however, the effects of such therapies on neutrophil activation have previously been poorly understood. We sought to evaluate neutrophil reactive oxygen species (ROS), especially H2O2 production, in the pathophysiology of sepsis or septic shock and the effect of CVVH or PMX-DHP on neutrophil ROS. Seven critically ill septic patients requiring CVVH (and 12 matched septic patients who did not require CVVH as control) and seven septic shock patients treated with PMX-DHP were studied. We found that patients with sepsis or septic shock had significantly higher levels of neutrophil ROS compared with normal volunteers (183 +/- 42, 292 +/- 90, and 103 +/- 30) ($P < 0.05$, and < 0.005). Neutrophil ROS did not change over time in patients treated either with CVVH or without CVVH. In contrast, neutrophil ROS significantly inhibited PMX-DHP treatment in patients with septic shock (pretreatment; 292 +/- 88 vs. post-treatment; 205 +/- 93, $P < 0.05$). In conclusion, neutrophil ROS was significantly enhanced in the sepsis or septic shock affected patients. CVVH did not affect neutrophil ROS while PMX-DHP significant inhibited neutrophil ROS.

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Removing endocannabinoids and reducing oxidative stress with polymyxin-B-immobilized fibers in patients with septic shock

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Introduction Arachidonylethanolamide (AEA) and 2-arachidonyl- glycerol (2-AG) are endocannabinoids involved in septic shock, and 8-epi prostaglandin F2α (F2-isoprostane) is a biomarker of oxidative stress. Because the antibiotic polymyxin-B binds to endotoxins and endocannabinoids, direct hemoperfusion therapy with polymyxin-B-immobilized fibers (PMX-DHP) decreases serum levels of endocannabinoids. To investigate the features of sepsis and to determine the proper usage of PMX-DHP, we compared perioperative changes in levels of endocannabinoids and F2- isoprostane in patients with septic shock
Methods Twenty-four patients with septic shock induced by peritonitis underwent laparotomy for drainage.

Endocannabinoid absorption with PMX-DHP was examined in two groups of patients: patients in whom systolic arterial BP had increased more than 20 mmHg (BP elevation group; n = 12) and patients in whom BP did not increase or had increased no more than 20 mmHg (BP constant group; n = 12).
Results Levels of AEA did not change after PMX-DHP in the either the BP constant group or the BP elevation group, whereas levels of 2-AG decreased significantly after PMX-DHP in the BP elevation group but not in the BP constant group (Figure 1). F2-isoprostane gradually increased after PMX-DHP. On the other hand, levels of F2- isoprostane remained constant in the BP elevation group (Figure 2).

Figure 1 (abstract P119)

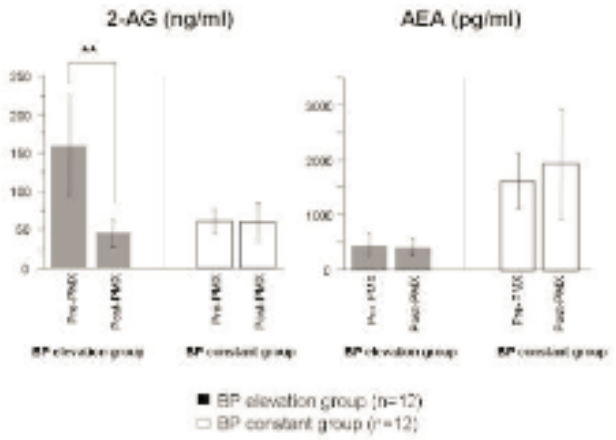
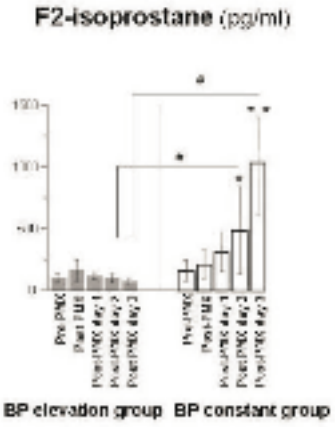


Figure 2 (abstract P119)



Conclusions Patients with septic shock are under considerable oxidative stress, and 2-AG plays an important role in the cardiovascular status of these patients. The removal of 2-AG by PMX-DHP benefits patients with septic shock by stabilizing cardiovascular status and decreasing long-term oxidative stress.

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The role of plasminogen activator inhibitor 1 measurement with endotoxin adsorption therapy (PMX-DHP) for postoperative septic shock patients

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Introduction A polymyxin B immobilized fiber column (PMX; Toray Industries Inc., Tokyo, Japan) was developed in Japan in 1994 and it has been used for treatment of endotoxemia or septic shock patients. Materials and methods All patients received an urgent operation due to intra-abdominal infection. In 88 cases treated with a poly- myxin B immobilized column through direct hemoperfusion (PMX- DHP), changes in hemodynamics, pulmonary oxygenation (PaO2/ FIO2) and various mediators (IL-6, IL-8, IL-ra, plasminogen activator inhibitor 1 (PAI-1)) were examined before and after PMX-DHP, stratifying with the outcome (64 survivors and 24 who died). PMX- DHP was performed through a double lumen catheter (11.5 Fr), placed in the femoral vein or internal jugular vein, at a blood flow rate of 80 ml/min using nafamostat mesilate as an anticoagulant for 2 hours.
Results PMX-DHP significantly increased systemic arterial pressure and mean arterial pressure, with a greater increase in the survival group. Also, there appeared to be a trend for PaO2/FIO2 improve- ment as blood pressure increased. As the mechanism for improve- ment of pulmonary oxygenation by PMX-DHP has not been shown clearly, it remained to be examined further. PAI-1 values significantly decreased in the survivor group (from 436 ± 549 to 251 ± 283 ng/ml) immediately after PMX-DHP; also intracellular adhesion molecule-1 and endothelial leukocyte adhesion molecule- 1 tended to decrease in both groups.
Discussion PAI-1 is elevated by endotoxin, thrombin and cytokines, and is an indicator of vascular endothelial cell activation. In septic dissminated intravascular coagulation from Gram-nega- tive bacilli, a massive amount of PAI-1 is produced on vascular endothelial cells along with elevation of cytokine production and coagulation activity. In addition, PAI-1, one of the fibrinolysis inhibitory factors, plays an important role in regulating fibrinolysis by inhibiting tissue plasminogen activator, which converts plasminogen to active plasmin on fibrin, to block unnecessary fibrinolysis.
Conclusion The determination of PAI-1 may be a useful clinical parameter for predicting PMX-DHP efficacy.

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Mechanism and effectiveness of polymyxin B-immobilized fiber columns for removing mediators (HMBG-1, 2-arachidonoyl glycerol, anandamide, PAI-1, protein C and IL-6) in septic shock patients

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Introduction Septic shock remains a major cause of multiple organ failure with a high mortality rate. To remove an endotoxin in patient plasma, direct hemoperfusion (DHP) using a polymyxin B- immobilized fiber column (PMX; Toray Industries Inc., Tokyo Japan) was developed in Japan in 1994 and has since been used for the treatment of septic shock. The precise role of PMX is not clear. Patients and methods We treated 27 septic shock patients using DHP-PMX. The patients were separated into two groups for analysis: those whose systolic blood pressure (SBP) increased by more than 30 mmHg immediately after DHP-PMX (15 cases), and those whose SBP did not increase by more than 30 mmHg after DHP-PMX (12 cases). Furthermore, the patients were separated into two other groups for analysis: those whose P/F ratio increased by more than 20% immediately after DHP-PMX (15 cases), and those whose P/F ratio did not increase by more 20% after DHP- PMX (12 cases). Mediators were measured at four points: before and after DHP-PMX, and 1 day and 3 days afterward.
Results The patient group consisted of 17 males and 10 females, 59.6±12.7 years old. The average APACHE II score was 27.2±9.1, and the average SOFA score was 11.7±5.2 before DHP-PMX. Nineteen patients survived and eight died. When the changes in PAI-1, protein C, ATIII, IL-6 and high mobility group box protein 1 (HMGB-1) were compared between the groups, only the HMGB-1 levels had improved significantly in the SBP increased group ($P = 0.0125$). The SBP increased significantly after DHP- PMX in the HMGB-1-improved group ($P < 0.0001$). An improvement in the P/F ratio and a reduction in 2-arachidonoyl glycerol during DHP-PMX were significantly correlated ($P = 0.0184$). Conclusion We showed that the circulation dynamics of septic shock patients can be improved by reducing HMGB-1 levels and that respiratory function can be improved by reducing 2- arachidonoyl glycerol levels using DHP-PMX.

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Intraoperative Endotoxin Adsorption as a New Therapeutic Option for Mycotic Aortic Aneurysm

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An 82-year-old man with a mycotic aortic aneurysm of the distal arch underwent urgent surgery because of sepsis. The infected aortic arch was excised, replaced with a rifampicin-bonded prosthetic graft, and covered with omentum. Direct hemoperfusion using polymyxin B-immobilized fiber (PMX-DHP) was intraoperatively carried out in parallel with the cardiopulmonary circuit. Intraoperative PMX-DHP dramatically reduced the level of plasma endotoxin, and ameliorated hemodynamic instability and oxygenation, resulting in smooth weaning from cardiopulmonary bypass. Intraoperative endotoxin adsorption is technically simple and easy, effective in hemodynamic stabilization, and so could be a new therapeutic option for mycotic aortic aneurysm.
Keyword: Endotoxin adsorption Mycotic aortic aneurysm PMX-DHP Polymyxin B-immobilized fiber Sepsis

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Vascular Endothelial Growth Factor and Soluble fms-like Tyrosine Kinase-1 in Septic Shock Patients Treated With Direct Hemoperfusion With a Polymyxin B-immobilized Fiber Column

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Sepsis is characterized by a systemic inflammatory response to a microbial pathogen. In sepsis, capillary permeability is a tightly regulated feature of microcirculation in all organ beds and is fundamentally altered. We investigated the vascular endothelial growth factor (VEGF) level as a vascular permeability factor and the soluble fms-like tyrosine kinase-1 (Flt-1) level as an antagonist of the VEGF receptors. Serum VEGF and soluble Flt-1 levels in 21 patients with septic shock, who were treated with direct hemoperfusion with a polymyxin B-immobilized fiber column (DHP-PMX), were measured by enzyme-linked immunoassay. The VEGF and the soluble Flt-1 levels were more elevated in patients with septic shock than in controls. Between 14 survivors and 7 non-survivors, there was no significant difference in VEGF level before the DHP-PMX therapy, but the soluble Flt-1 level of survivors was significantly lower than that of non-survivors. Although there was no significant difference between starting and ending VEGF levels in survivors, in non-survivors the VEGF level at the end of DHP-PMX therapy was significantly lower than that at the start. In survivors, the soluble Flt-1 level at the end of DHP-PMX therapy was significantly lower than that at the start. On the other hand, in non-survivors, there was no significant difference between the ending and starting soluble Flt-1 levels. The soluble Flt-1 level may be a suitable marker of disease severity and mortality.

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Urinary liver-type fatty acid-binding protein in septic shock: effect of polymyxin B-immobilized fiber hemoperfusion.

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We aimed to determine retrospectively whether urinary liver-type fatty acid-binding protein (L-FABP) levels are altered in patients with septic shock or severe sepsis without shock and whether polymyxin B-immobilized fiber (PMX-F) hemoperfusion affects these levels. Forty patients with septic shock, 20 patients with severe sepsis without shock, 20 acute renal failure (ARF) patients without septic shock (mean serum creatinine, 2.8 mg/dL), and 30 healthy volunteers were included in this study. Polymyxin B-immobilized fiber hemoperfusion was performed twice in 40 patients. In addition, 10 patients with septic shock without PMX-F treatment (conventional treatment) were also enrolled in this study. Their families did not choose PMX-F treatment. Thus, their informed consents to perform PMX-F treatment were not obtained. Septic shock or severe sepsis was defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee. Patients with septic shock were eligible for inclusion in the study if they had a definable source of infection and/or positive blood cultures. Patients with cardiogenic or hemorrhagic shock were excluded from the study. The patients were not randomly allocated to receive PMX-F treatment. Urinary and serum L-FABP levels were measured by enzyme-linked immunosorbent assay method. Plasma endotoxin levels in patients with septic shock were significantly higher than those in patients with severe sepsis ($P < 0.05$), patients with ARF ($P < 0.001$), and healthy subjects ($P < 0.001$). Urinary L-FABP levels in patients with septic shock were significantly higher than those in patients with severe sepsis without shock ($P < 0.001$), patients with ARF ($P < 0.001$), and healthy subjects ($P < 0.001$), whereas serum L-FABP levels showed no significant differences between patients with septic shock, patients with severe sepsis, patients with ARF, and healthy subjects. Urinary L-FABP was not correlated with serum L-FABP. Twenty-eight patients with septic shock survived, and 12 patients died. Polymyxin B-immobilized fiber treatment reduced plasma endotoxin levels ($P < 0.01$) and urinary L-FABP levels ($P < 0.01$). In 10 patients with septic shock without PMX-F treatment, L-FABP levels remained high 7 days after initiation of conventional treatment ($P = 0.12$). These results suggest that urinary L-FABP levels are significantly increased in patients with septic shock and that PMX-F treatment is effective in reducing these levels.

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Direct hemoperfusion with polymyxin-B-immobilized fiber columns improves septic hypotension and reduces inflammatory mediators in septic patients with colorectal perforation.

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PURPOSE: Although some studies have reported favorable effects of direct hemoperfusion with polymyxin-B-immobilized fiber columns (PMX) for the treatment of septic shock, few studies have demonstrated the efficacy of PMX in studies with a uniform case definition and without any other blood purification techniques. MATERIALS AND METHODS: Fifty-two patients with severe sepsis or septic shock secondary to colorectal perforation were treated with PMX. Hemodynamic alterations and plasma concentrations of endotoxin, interleukin (IL)-1beta, IL-1 receptor antagonist (IL-1Ra), IL-6, IL-8, and IL-10 were evaluated following PMX treatment. RESULTS: We observed a significant reduction in plasma endotoxin in the nonsurvivors immediately after PMX treatment compared to before treatment. Systolic blood pressure was markedly increased and circulating levels of IL-1beta, IL-1Ra, and IL-8 were significantly reduced during a 2-h interval of PMX. CONCLUSIONS: Our findings suggested that PMX treatment appears to adsorb endotoxin and also modulates circulating cytokine during a 2-h interval of direct hemoperfusion in septic patients with such condition.

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Clinical experience with a novel endotoxin adsorbtion device in patients undergoing cardiac surgery

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Endotoxaemia is thought to occur in cardiac surgery using extracorporeal circulation (ECC) and a positive correlation has been proposed between the magnitude of endotoxaemia and risk for postoperative complications. We studied the effects of a new endotoxin adsorber device (Alteco® LPS adsorber) in patients undergoing cardiac surgery with ECC, with special reference to safety and ease of use. Fifteen patients undergoing coronary artery bypass and/or valvular surgery were studied. In 9 patients, the LPS Adsorber was included in the bypass circuit between the arterial filter and the venous reservoir. Flow through the adsorber was started when the aorta was clamped and stopped at the end of perfusion. Flow rate was kept at 150 ml/min. Six patients served as controls with no adsorber in the circuit. Samples were taken for analysis of endotoxin, TNFα, IL-1ß and IL-6 as well as complement factors C3, C4 and C1q. Whole blood coagulation status was evaluated using thromboelastograpy (TEG) and platelet count. No adverse events were encountered when the adsorber was used in the circuit. Blood flow through the device was easily monitored and kept at the desired level. Platelet count decreased in both groups during surgery. TEG data revealed a decrease in whole blood clot strength in the control group while it was preserved in the adsorber group. Endotoxin was detected in only 2 patients and IL-1ß in 4 patients. IL-6 decreased in both groups whereas no change in TNF concentrations was found. C3 fell in both groups, but no changes wer found in C4 and C1q. The Alteco® LPS adsorber can be used safely and is easy to handle in the bypass circuit. No complications related to the use of the adsorber were noted. The intended effects of the adsorber, i.e. removal of endotoxin from the blood stream could not be evaluated in this study, presumably due to the small number of patients and the relatively short perfusion times.
Key Words: adsorbtion • cardiopulmonary bypass • endotoxin • inflammatory mediators

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The Treatment of Severe Sepsis and Septic Shock by Continuous Hemodiafiltration Using a PMMA Membrane Hemofilter

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Abstract
A wide variety of blood purifications intended for removal of humoral mediators such as cytokines are performed in patients with severe sepsis/septic shock. While high-volume hemofiltration (HVHF), hemofiltration using high cut-off membrane filters, and direct hemoperfusion with an immobilized polymyxin-B column (PMX-DHP) are representative types of this treatment, we perform continuous hemodiafiltration using a polymethylmethacrylate membrane hemofilter (PMMA-CHDF), which features excellent cytokine-adsorbing capacity, for the treatment of severe sepsis/septic shock. PMMA-CHDF efficiently removes various cytokines from the bloodstream, resulting in early recovery from shock and a high survival rate. PMMA-CHDF also removes anti-inflammatory cytokines from the blood stream, suggesting that it might improve immunoparalysis as well. These findings suggest the clinical usefulness of PMMA-CHDF intended for cytokine removal in severe sepsis/septic shock.

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New sepsis-related marker: endotoxin activity assay

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Introduction The endotoxin activity assay (EAA) is a rapid whole-blood chemiluminescent test for endotoxin that has proven clinical utility in the detection and risk stratification of clinically ill patients with suspicion of sepsis.
Methods The EAA was studied in a cohort of 153 septic patients admitted to the ICU. At the same time, IL-6 (chemiluminescent enzyme immunoassay), C-reactive protein (CRP), procalcitonin (PCT, chemiluminescent enzyme immunoassay) and plasminogen activator inhibitor-1 (PAI-1, latex photometric immunoassay) were measured within 24 hours after ICU admission. The patients were divided into the following three groups: L group: EAA <0.4, M group: 0.4 ≤EAA <0.6, H group: 0.6 ≤EAA. Nonrepeated- measures ANOVA was used to compare over three groups or conditions. Statistical significance was assumed for values of P <0.05. Normally distributed data are presented as mean ± SD, and abnormally distributed data are presented as median values.
Results Of the 153 patients, the L group contained 61 patients, M group 41 patients, and H group 51 patients, respectively. On the day of ICU admission, the rate of EAA ≥0.4 was 60.1% (MEDIC study: 57.2%). APACHE score in the L group was 21.0 ± 7.9, M group 24.8 ± 8.4, H group 26.4 ± 8.9, and SOFA score in the L group was 8.2 ± 4.3, M group 8.9 ± 4.1, H group 9.5 ± 4.3, respectively. There was no statistically significant difference among the groups. The median value of PCT in the L group was 1.1 ng/ml, M group 5.9 ng/ml, H group 8.5 ng/ml, respectively. PCT values of the M and H groups were significantly higher than those of the L group. Median IL-6 level of the H group was significantly higher than that of the L group (H group: 2,635 pg/ ml, L group: 177 pg/ml).
Conclusions EAA has no significant correlation with other sepsis-related markers, but may be associated with body insults (inflammation or infection).

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Lipopolysaccharide is required for leukocyte adhesion to Toraymyxin® filters used in the treatment of sepsis

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Introduction Extracorporeal hemoperfusion with polymyxin B is a novel septic treatment, shown to improve hemodynamics, organ dysfunction, and mortality through the removal of circulating lipopolysaccharide (LPS). This therapy can also remove activated leukocytes, which likely contributes to reduced inflammation and improved patient

outcome; however, the mechanistic role of LPS in the removal of leukocytes remains unclear. Objective To determine whether the presence of LPS and/or activation of leukocytes by LPS alters their ability to bind to polymyxin-bound filters used for extracorporeal hemoperfusion of septic patients.
Methods Toraymyxin® filters were opened under sterile conditions and 2 cm2 sections were incubated for 2 hours under various conditions. Experiment 1: filters were exposed to (1) whole blood collected from a health volunteer, (2) blood with 700 ng/ml LPS (Escherichia coli 0127:B8), or (3) blood pre- incubated for 2 hours in 700 ng/ml LPS. Experiment 2: filters were pre-exposed to LPS then incubated with blood alone or blood with LPS. Experiment 3: filters were exposed to blood containing increasing LPS concent
rations (1 pg/ml to 500 ng/ml) or TNFα (15 pg/ml to 10 ng/ml). In all experiments, following incubation, filters were washed, stained (methylene blue + eosin) and the number of adhered leukocytes were counted by light microscopy. Endotoxin activity of the collected whole blood in both the absence and presence of LPS was determined by an endotoxin activity assay (EAATM).
Results The presence of LPS significantly increased (3.77 ± 0.54-fold, P = 0.005) the number of adhered leukocytes to Toraymyxin® filters. Moreover, pre-incubation of the blood with LPS, to activate inflammatory cells, further increased leukocyte adhesion (7.59 ± 1.08-fold increase vs. control, P = 0.002,

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Endotoxin Activity Assay and Polimyxyn-B in early management of endotoxemia

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The aim of this study was to evaluate the ability of the Endotoxin Activity (EA) assay to determine the need for early intervention of endotoxemia using polymyxin-B based hemoperfusion (PMX-DHP) on septic patients. The secondary end point to highlight the major incidence of endotoxin activity in transplant patients. Methods: From April 2008 to October 2009, fourty-one patients after surgical period with diagnosis of SIRS were enrolled in this study. Cause of surgery: major abdominal surgery 22 patients(pt); liver transplant 14pt; kidney transplant 3pt and lung transplant 2pt. Nineteen patients had a high EA level (≥ 0.6) and were treated with PMX-DHP every 24 hours until the EA level was low (< 0.4). The remaining twenty-two had EA levels <0.60 and received standard therapy only. Results: Twenty-two (55%) showed a low endotoxin activity level (EA < 0.6) at the first examination. These levels did not significantly change after 24 hours except one patient. This patient showed an EA of 0.62 after 24 hours and was then shifted to the treatment group. Microbiological findings of these patients in the low endotoxin level group, showed the presence of Gram positive infections in 14 of 22 patients, 5 infections of mycetes and three fungal infections. Of the 19 patients(45%) with EA> 0.60, 25% had abdominal surgery; 70% had liver transplant; 66% kidney transplant and 50% lung transplant. Among patients showing EA≥0.6, seven patients (median EA=0.64 [0.62-0.87) required two PMX-DHP treatments, nine patients (median EA=0.845 [0.74–1.08]) required three treatments and three patients (median EA=0.985 [0.72–1.25]) required four treatments in order to reach EA<0.4 condition (median 0.328 (range [0.22-0.48]). No adverse events were observed during the hemoperfusion treatments performed. At the end of the PMX-DHP therapy, a statistically significant improvement in the hemodynamic parameters, Mean Arterial Pressure (MAP) and Heart Rate (HR), were observed. White blood cells count significantly decreased and the PaO2/FiO2 ratio increased. Median SOFA scores also decreased from 7 (range [3-13]) to 4 (range[1-12]) at the end of the therapy. Conclusion: The EA assay can identify patients eligible for PMX-DHP treatment and aids its therapeutic dosing.

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Endotoxin Activity Assay (EAA) and Polymyxin-B hemoperfusion (PMX-DHP)- an endotoxin targeted theranostic strategy

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Introduction : Endotoxin (LPS) is a lethal mediator of critical illness. In the EUPHAS trial (JAMA 2009), PMX-DHP was shown to decrease mortality in patients with septic shock.
Patients were selected on clinical grounds due to the lack of a tool to reliably measure LPS in vivo. The combination of a clinically useful assay to measure LPS in blood, linked to a specific therapy provides an important theranostic advance for critically ill patients with endotoxemia. We tested (a) the laboratory robustness of the EAA, and (b) its

clinical utility to select responders of PMX-DHP.
Methods: (a) Robustness was defined as resistance to external contamination while providing clinically relevant information. Healthy donor samples (n=8) were assayed before and after exogenous contamination with 230 pg/mL and 1000 pg/mL of E. Coli O55:B5 LPS into the reagents. (b) Clinical utility was tested in an observational study of the EAA (7 centers, Japan, 2007-08. 47 critically patients were selected for PMX-DHP therapy (61 treatments). EAA was drawn at baseline and 12 hours after PMX-DHP). **Results:** (a)Healthy donor baseline EAA 0.24 (mean) and following the addition of 230pg/ml, 0.22 EAA units and 0.26 units following addition of 1000pg/mL. There were no significant differences in EAA values following addition ofexogenous LPS.(b) Mean EAA prior to PMX-DHP was 0.65 units (+/- 0.22) at 12 hours the mean EAA value was 0.45 (+/-0.17) [p<0.010].
Conclusions : The EAA is a robust and rapid (30 min) test for LPS and is resistant to external contamination and is readily applicable for routine clinical practice. This theranostic represents an attractive opportunity to remove endotoxin in patients with proven endotoxemia and may result in improved outcomes. Work supported by Spectral Diagnostics Inc

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Effects of Direct Hemoperfusion with Polymyxin B Immobilized Fiber (PMX-DHP) for Patients with Septic Multiple Organ Failure

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For patients with septic shock/septic multiple organ failure, Early Goal-Direct Therapy using direct hemoperfusion with polymyxin B immobilized fiber (PMX-DHP) brings about a significant improvement in circulation, respiratory condition and multiple organ survival evaluated by the SOFA score. It is suggested that its mechanism involves modulating mediators, such as endogenous cannabinoids, cytokines and HMGB-1, and controlling the biological response. In recent years, many reports from foreign countries concerning PMX-DHP have been published. PMX-DHP is a useful and effective treatment method, so the evaluation of PMX-DHP must be performed inside and outside the country. In the future, it is expected that PMX-DHP treatment will be incorporated in the treatment strategy of septic shock and septic multiple organ failure around the world.

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A 6-year-old child with idiopathic gastric rupture leading to septic shock, who responded well to PMX (endotoxin adsorption using polymyxin-B immobilized fiber) and CHDF (continuous hemodiafiltration)

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We report 6-year-old boy who developed severe vomiting with upper abdominal pain after lunch on June 26, 2007, and then abdominal distention appeared the following day. After consulting a local physician, he was referred to the pediatric division of our hospital and admitted for examination and treatment. Because the patient was in shock with a high fever and tachypnea, he was placed in ICU for total body management. Abdominal CT showed a large amount of free air and ascites, enlarged stomach, duodenum, and small intestine. Perforation of the upper digestive tract was assumed and emergent abdominal surgery was performed. Based on intraoperative findings of ascites along with a rupture on the back wall of the proximal greater curvature of the upper section of the stomach and food residue in the abdominal cavity, peritonitis due to the gastric rupture was diagnosed and partial gastric resection including the ruptured section was carried out. After surgery, the patient remained in septic shock state with a systolic blood pressure of 60mmHg despite administration of dopamine (DOA). Therefore, endotoxin adsorption using polymyxin-B immobilized fiber (PMX) was carried out. The blood pressure rapidly increased after PMX was initiated, and improved to 136/70mmHg after 2 hours. After completing PMX, treatment was switched to continuous hemodiafiltration (CHDF) and sufficient diuresis could be obtained. Three days later, both of DOA and CHDF were discontinued. The patient was discharged from ICU on July 27, and discharged from hospital on December 22. In

later childhood, idiopathic gastric rupture is rarely observed, and this is the third case of septic shock treated by PMX to be reported in Japan. Consideration of the need for blood purification therapy, which includes PMX, is recommended in order to achieve early withdrawal from severe septic shock and improvement of the total body condition, even in pediatric cases.
Key words: idiopathic gastric rupture, septic shock, endotoxin adsorption, continuous hemodiafiltration

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Management of Sepsis During MARS Treatment in Acute on Chronic Liver Failure

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Introduction: The aim of our study was a 30-day follow-up of the use of early detection of endotoxin by the endotoxin activity assay (EAA) for patients with acute liver failure superimposed on chronic liver disease (AoCLF) and treated with polymyxin-B hemoperfusion-based (PMX-DHP) treatment and albumin dialysis in the molecular adsorbent recirculating system (MARS).
Materials and Methods: From February 2008 to July 2010, we evaluated 10 AoCLF patients experiencing systemic inflammatory response syndrome (SIRS) in association with suspected infection and an EAA-positive test (>0.60). These patients awaiting liver transplantation (OLT) showed similar Model End-Stage Liver Disease (MELD) scores (range, 19–25) and encephalopathy grade ≤ 2. Five patients received therapy to remove endotoxins with PMX-DHP with MARS treatment for liver failure (group A); the other 5 patients received MARS treatment only (group B).
Results: Two PMX-DHP treatments were performed in 4 group A patients (average EA = 0.66 [range, 0.61–0.70]) and 3 treatments for 1 patient (EA = 0.92). All 5 subjects underwent an average of 4 MARS treatments (range, 3–5). At the end of therapy, the median EA level was 0.42 (range, 0.37–0.48). As reported in the literature, we achieved a significant improvement in liver and kidney functions using MARS. Measurements of lactate, interleukin (IL)-6, and tumor necrosis factor (TNF)-α were significantly improved among patients treated with the extracorporeal therapies. At 30 days of observation, all 5 patients treated with MARS plus PMX-DHP are alive. In group B, a mean of 7.5 MRAS treatments were performed. We observed an improvement in hemodynamic and liver functions with reduced levels of proinflammatory cytokines and lactates in 4 patients. One patient showed no improvement in clinical status with the development of sepsis and subsequent multiorgan failure after 24 days.
Conclusion: The possibility of an early diagnosis using the EAA in AoCLF patients could prevent the progression of the sepsis cascade. The use of PMX-DHP and MARS in these patients, could lead to resolution of clinical status in a short time.

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Polymyxin B-Immobilized Fiber Column Hemoperfusion Therapy for Septic Shock.

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Endotoxin, an outer membrane component of Gram-negative bacteria, plays an important role in the pathogenesis of septic shock. Endotoxin adsorption therapy by polymyxin B-immobilized fiber column hemoperfusion (PMX) has been used for the treatment of septic shock patients in Japan since 1994. The covalent binding of polymyxin B onto the surface of the polystyrene-based carrier fiber in PMX inactivates the endotoxin in the blood without exerting toxicity. This study was performed as a systematic review to evaluate the efficacy and mechanism of PMX treatment in patients with septic shock. The PubMed database and references from identified articles were used to search and review the literature relating to the efficacy and mechanism of PMX treatment in patients with septic shock. PMX adsorbed monocytes, activated neutrophils, and anandamide as well as endotoxin through direct covalent bond, hydrophobic and ionic interactions, and hydrodynamics, and reduced the blood concentrations of inflammatory cytokines, plasminogen activator inhibitor (PAI)-1 and adhesion molecules. PMX increased blood pressure and reduced the dosage requirements for vasopressive/inotropic agents. The meta-analysis showed that PMX treatment had beneficial effects on the hemodynamics, pulmonary oxygenation, and mortality. These beneficial effects may be attributable to the direct adsorption of endotoxin, monocytes, activated neutrophils, and anandamide, as well as

indirect decrease in inflammatory cytokines and other mediators. PMX treatment has additional effects on reducing endothelial damage, proapoptotic activity and immunosupression. Further studies will be needed to confirm the efficacy and mechanism of PMX treatment in septic shock.
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EAA HELPS TO DETECT THE CAUSE OF ARDS AT BED SIDE

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Introduction: It is known that several serum markers are useful as a prognostic factor in septic patients. Endotoxin Activity Assay (EAA) is a first reported as a method for detecting endotoxin based on the ability of antigen-antibody complex to prime neutrophils and augmented respiratory burst response. Endotoxin assay (EA) levels were expressed in relative units derived from the integral of the basal (no antibody) and stimulated (4600pg/ml LPS) chemiluminescent response. Several reports have shown that EA levels were significantly increased in septic patients.The most common predisposing causes of ARDS are sepsis, pneumonia and aspiration.The ARDS on the basis of pneumonia include infectious pneumonia with sepsis and noninfectious pneumonia such as interstitial pneumonia and aspiration pneumonitis. Whereas it is clear that the treatment for ARDS caused by infectious pneumonia with sepsis is the administration of the antibiotics, most cases of noninfectious pneumonias seem to respond to the early initiation of systemic corticosteroid.Although it is important to find the cause of ARDS on the basis of pneumonia, there was no report to show that serum biomarkers distinguish between infectious and noninfectious pneumonia.Since radiologic findings in ARDS patients show bilateral parenchymal infiltrates, it is difficult to distinguish the cause of ARDS definitely between infectious and noninfectious pneumonia.
Hypothesis: EAA may be an appropriate method for distinguishing the cause of ARDS between infectious pneumonia with sepsis and noninfectious in serum biomarkers.
Methods: 12 patients, who were fulfilled the diagnostic criteria for ARDS during our ICU stay from Sep.2009 to Aug.2010 and who did not have an organ disorder except for lung, were included. Blood was sampled at the first day fulfilled our criteria for measuring WBC, CRP, Procalcitonin (PCT) and EAA . After the serious search for the cause of ARDS, such as tuberculosis, atypical mycobacteriosis and atypical pneumonia, 6 patients were infectious pneumonia and the other 6 patients were noninfectious. Bacteria were cultured in all 6 patients of infectious pneumonia. There were 4 patients of interstitial pneumonia and 2 patients of chemical pneumonitis by aspiration in noninfectious pneumonia.
Results: There was no significant difference of WBC count, CRP and PCT levels between infectious pneumonia and noninfectious.In contrast, all patients of infectious pneumonia presented >0.40 unit of EA and all patients of noninfectious presented <0.40. Infectious pneumonia showed significantly higher levels of EA compared to noninfectious.
Conclusions: EAA may be an appropriate method for distinguishing the cause of ARDS between infectious pneumonia with sepsis and noninfectious at bed side.

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SYSTEMIC ENDOTOXEMIA FOLLOWING MULTIPLE TRAUMA IS ASSOCIATED WITH EARLY SHOCK AND PREDICTS SUBSEQUENT MORTALITY

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Background: Multiple trauma is associated with innate immune activation and inflammatory morbidity, even in the absence of superimposed infection. The potential etiologic role of bacteria or bacterial endotoxin (LPS) translocating from the gut has been controversial. We undertook a serial evaluation of circulating LPS levels in a cohort of trauma victims.
Methods: We performed a prospective observational cohort study of patients sustaining severe multiple trauma (ISS>16). We measured LPS levels on days 0, 1, 3, and 5 using the Endotoxin Activity (EA) Assay® - a whole blood assay based on LPS-primed neutrophil chemiluminescence that quantifies endotoxin on a scale from 0 to 1.0 activity (EA) units. EA levels were stratified as low (< 0.40 EA units), intermediate (?0.40-0.59 EA units), or high (?0.60 EA units). We collected data on demographics, resuscitation, length of stay (LOS), and mortality. Statistical analyses used ANOVA, Fisher's exact or Student t tests, as appropriate, with an ? level of $p<0.05$.
Results: We recruited 22 patients having a mean age of 43?23 years and mean ISS of 40?15. Most (82%) were male, and 17/22 had sustained blunt trauma. We analyzed only those patients having a minimum of three EAA

values (N=20). Their median ICU LOS was 9 days (2-29) and their duration of mechanical ventilation, 9 days (1-27). Four patients died (20%) at 10±1 days post admission. The mean initial (Day 0) EA value was low, but increased significantly over time (Table; ANOVA for trend p=0.0013). Maximal EA values were reached at an average of 80±40 hours; four (20%) patients recorded high EA levels, while in 12 (60%) the maximal levels were intermediate. EA levels exceeded 0.4 on at least 2 occasions in all 4 non-survivors, but in only 3/16 survivors (p=0.007). Both maximal EA levels (0.65±0.15 vs 0.45±0.11; P=0.009), and average EA across Day 0 to Day 5 (0.48±0.06 vs 0.32±0.10; P=0.008) were higher in non-survivors than in survivors. The average EA level correlated significantly with the presence of shock at admission (r2= 0.2; P=0.04).
Conclusion: Endotoxemia is not present immediately following trauma, but develops over time during the early post-injury period. Its presence predicts adverse outcome. The association of endotoxemia with systemic hypoperfusion suggests that the GI tract is the source of circulating endotoxin in the victim of multiple trauma.

Table:

	Day 0	Day 1	Day 3	Day 5
Time to EA (h); mean (SD)	13.6(6.8)	35.1(7.6)	84.0(8.4)	132.2(7.5)
EA level (u); mean (SD)	0.24(0.12)	0.35(0.12)	0.42(0.10)	0.42(0.13)
* EA ≥ 0.4	5%	40%	55%	56%
* Max EA	5%	30%	35%	30%

* Proportion of patients at each sampling time.

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Hemoperfusion Treatment in a Septic Shock Patient with Autosomal Dominant Polycystic Kidney Disease and Increased HMGB1 Protein Levels.

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This case report describes polymyxin B-immobilized fiber (PMX-F) treatment of septic shock caused by pyelonephritis in a 68-year-old woman with autosomal dominant polycystic kidney disease. She was admitted for severe lower left abdominal pain, high fever (40°C) and gross hematuria. Her endotoxin and high-mobility group box-1 protein (HMGB1) levels were extremely elevated. Her blood pressure was 68/36 mm Hg. Urinalysis revealed innumerable white blood cells (WBCs). Blood and urine cultures were positive for Klebsiella pneumoniae and Pseudomonas aeruginosa. Plain abdominal radiography showed large kidney shadows and calcium deposition. Septic shock with endotoxemia was diagnosed. Her symptoms of septic shock persisted for 3 days with antibiotics, γ-globulin and dopamine. Direct hemoperfusion was performed twice with a PMX-F column. The patient's body temperature, WBC count and C-reactive protein level decreased. Her blood endotoxin level and blood HMGB1 level also decreased to an almost normal level. She was discharged on day 23 after admission.

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Evaluation of Different Perfusion Durations in Direct Hemoperfusion with Polymyxin B-Immobilized Fiber Column Therapy for Acute Exacerbation of Interstitial Pneumonias.

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Background: Recently, the potential therapeutic effect of direct hemoperfusion with a polymyxin B-immobilized fiber column (PMX-DHP) has been reported for acute exacerbation of interstitial pneumonia (AE-IP), a highly morbid clinical event; however, there is no consensus on the appropriate procedure for PMX-DHP. We examined the

appropriate perfusion duration of PMX-DHP for AE-IP. Methods: AE-IP patients receiving PMX-DHP were divided into two groups: short-duration group (≤6 h)(n = 5) and long-duration group (12 h)(n = 12). Results: ThePaO(2)/FiO(2)(P/F) ratio increased immediately after PMX-DHP in the two groups. In the long-duration group, the P/F ratio continued to increase over the following 7 days, while, in the short-duration group, the P/F ratio declined again 3 days after therapy. The survival rate 30 days after PMX-DHP was significantly higher in the long-duration group than in the short-duration group. Conclusions: A long perfusion duration of PMX-DHP is more efficacious for AE-IP than a short perfusion duration.

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[A meta-analysis of the effects of direct hemoperfusion with polymyxin B-immobilized fiber on prognosis in severe sepsis.]

[Article in Chinese]

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OBJECTIVE: To investigate the effects of direct hemoperfusion with polymixin B-immobilized fiber (DHP-PMX) in patients with sepsis.
METHODS: We searched Pubmed, Embase, Web of Science databases and identified relevant randomized controlled trials (RCT) from January 1995 to May 2010. Meta-analysis of DHP-PMX on mortality and levels of endotoxin in patients with sepsis were conducted using the methods recommended by the Cochrane Collaboration.
RESULTS: Eleven RCTs were included. Eight of them included the mortality of patients (sample size: 211 DHP-PMX and 178 conventional medical therapy). In total, the mortalities of patients with sepsis in DHP-PMX group and conventional group were 37.4% (79/211) and 68.5% (122/178) respectively. Compared with the conventional medical therapy, DHP-PMX appeared to significantly reduce mortality (OR = 0.24, 95%CI 0.16 - 0.38, P < 0.000 01). The results were similar when two RCTs enrolling patients with methicillin resistant staphylococcus aureus (MRSA) infections were excluded (OR = 0.27, 95%CI 0.17 - 0.45, P < 0.000 01). When the analysis was limited to the nine studies that reported 28- to 30-day mortality, results were unchanged (OR = 0.29, 95%CI 0.17 - 0.48, P < 0.000 01). Six RCTs had the available data of endotoxin. The level of endotoxin decreased 31 ng/L(95%CI 22.46 - 39.55) after DHP-PMX therapy, and the decreasing was statistically significant (P < 0.000 01), while the level of endotoxin in patients of conventional group did not change (P = 0.94).
CONCLUSIONS: This study suggests a favorable effects of DHP-PMX on mortality and endotoxin decreasing in patients with sepsis. However, lack of enough cases and blinding need to be considered. Further investigation with large sample of high quality RCTs is needed.

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Hemoperfusion Treatment in a Septic Shock Patient with Autosomal Dominant Polycystic Kidney Disease and Increased HMGB1 Protein Levels

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This case report describes polymyxin B-immobilized fiber (PMX-F) treatment of septic shock caused by pyelonephritis in a 68-year-old woman with autosomal dominant polycystic kidney disease. She was admitted for severe lower left abdominal pain, high fever (40°C) and gross hematuria. Her endotoxin and high-mobility group box-1 protein (HMGB1) levels were extremely elevated. Her blood pressure was 68/36 mm Hg. Urinalysis revealed innumerable white blood cells (WBCs). Blood and urine cultures were positive for Klebsiella pneumoniae and Pseudomonas aeruginosa. Plain abdominal radiography showed large kidney shadows and calcium deposition. Septic shock with endotoxemia was diagnosed. Her symptoms of septic shock persisted for 3 days with antibiotics, γ-globulin and dopamine. Direct hemoperfusion was performed twice with a PMX-F column. The patient's body temperature, WBC count and C-reactive protein level decreased. Her blood endotoxin level and blood HMGB1 level also decreased to an almost normal level. She was discharged on day 23 after admission.

Key Words: Polymyxin B-immobilized fiber; Autosomal dominant polycystic kidney disease; Endotoxin; High-mobility group box-1 protein; Sepsis

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Efficacy of endotoxin absorption therapy on sepsis by polymyxin B-attached fibers

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Introduction Endotoxin plays a role in the development of Gram- negative bacterial sepsis. In Japan, polymyxin B-attached fibers (PMX-B) are used clinically as an endotoxin absorption therapy to neutralize the biological activity of lipid A, the immunomodulatory center of lipopolysaccharide (LPS) endotoxin. Because hemodynamic improvement is not seen in all cases, it cannot be assumed that this therapy will be effective against all cases of sepsis.
Hypothesis Endotoxin absorption therapy is effective against abdominal infection. Moreover, the mortality rate significantly improved in endotoxin-positive cases of abdominal infection. Methods Between 1997 and April 2008, endotoxin absorption therapy was performed on 105 septic patients in the ICU of Hyogo College of Medicine and the Osaka City General Hospital. The 105 cases were divided into an abdominal infection group (n = 45) and a nonabdominal infection group (n = 60). Before and after therapy, the endotoxin level was measured in patients using the limulus amoebocyte lysate (LAL) and endotoxin activity assay (EAA) methods. Moreover, we measured blood pressure, cardiac index, and the administered dose of catecholamine. Using a retrospective analysis, we compared Sequential Organ Failure Assessment (SOFA) scores; the Risk, Injury, Failure, Loss, and End stage (RIFLE) criteria; and the 28-day survival rate between the two groups. Results After the endotoxin absorption therapy, mean blood pressure increased significantly from 67.9 ± 11.4 to 86.4 ± 6.3 mmHg in the abdominal infection group, whereas there was no change in the nonabdominal infection group. After the therapy, the SOFA scores and RIFLE criteria improved in both groups, but they improved significantly in the abdominal infection group. Patients in the abdominal infection group, especially the endotoxin-positive cases, recovered earlier from shock and had a significantly higher rate of survival than the abdominal infection group. Conclusion In endotoxin-positive patients with an abdominal infection, absorption therapy improved survival rate and cardiac and renal dysfunction due to sepsis or septic shock. However, further studies are required to verify the effectiveness of endotoxin absorption therapy.

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Investigation into problems associated with the endotoxin activity assay

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Introduction Endotoxin activity assay (EAA) levels were compared with endotoxin levels determined by the turbidimetric kinetic method. Methods A specific method for the measurement of endotoxin, in the blood of patients under various conditions, and the influence of steroids on EAA levels and contamination of tubes used for the measurements were investigated.
Results EAA levels increased in patients with injuries and acute pancreatitis. EAA levels did not increase in patients infected with Gram- positive bacteria. Endotoxin levels determined by the turbidimetric kinetic method did not increase in patients with injuries and acute pancreatitis and Gram-positive bacteria. When patients with long- term steroid use developed shock due to infection with Gram-negative bacteria, EAA levels did not increase but endotoxin levels determined by the turbidimetric kinetic method increased. EAA levels, but not endotoxin levels determined by the turbidimetric kinetic method, were suppressed by giving steroids in vitro. Endotoxin was detected in the tubes used for the measurements. This was suppressed by the addition of polymyxin B and anti-factor C antibody. EAA levels tended to increase immediately after direct hemoperfusion using a polymyxin- B-immobilized fiber column (PMX-DHP).
Conclusion Our findings suggest that the EAA had limitations as a method to measure endotoxin.

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A sepsis progression model in humans: characterization of biomarkers descriptive of sepsis progression

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Introduction Previously our group has developed neural net progression models to characterize the development of organ failure in an ovine only as well as an integrated human/ovine model of acute lung injury using early clinical information. The goal of this study was to expand our model of disease progression using clinically available data as well as more exploratory biomarkers, such as the endotoxin activity assay (EAA), cytokines, D-dimer, copeptin, and procalcitonin, in an adult population with sepsis. Methods Three North American study sites enrolled adult patients within 24 hours of meeting at least two SIRS criteria with clinical evidence of infection. Biomarker sampling occurred daily on days 1 to 7 and on days 14, 21, and 28. Clinical data from the 24 hours preceding the first sampling point as well as the baseline biomarker values were used as model inputs. Model outputs were serum creatinine (Scr) and organ metric (OM) over the study duration. OM is a composite parameter similar to the SOFA score with the CNS category removed and a continuous rather than categorical value. A neural net was used to perform a multiple parameter logistic regression while allowing for non-linear (usually sigmoidal) dependence on input parameters. Input parameters are first used individually to model the output and are then ranked based on the minimum mean squared error (MMSE) in these single-parameter models. The two parameters with the lowest MMSE are used to create the final multi-parametric model, which yields a lower modeling error than the original single-parameter models. Results Thirty patients were enrolled with the two most common infection types being pneumonia and bloodstream. Seventy per cent of patients had at least one organ failure at enrollment. Diastolic blood pressure (DBP), red blood cell count (RBC), and copeptin had the smallest MMSE when individually predicting OM. Combining DBP and RBC yielded good agreement between the modeled and actual OM value ($r^2 = 0.60$). Individually, the prothrombin time (PT), copeptin, and phosphorus had the smallest MMSE when modeling Scr. The r^2 value between the model and actual Scr was 0.64 when combining PT and copeptin.
Conclusion When analyzed using a neural net model, changes in overall organ dysfunction and serum creatinine were predicted from early clinical data in a population of adult patients with sepsis. Identifying predictive biomarker patterns and coupling this information with known drug/intervention response could aid in optimizing treatment timing for greatest clinical benefit.