Eur J Dermatol 2006; 16 (4): 423-7

Takaharu IKEDA[1]
Shoko KANEHARA[2]
Toshio OHTANI[1]
Fukumi FURUKAWA[1]

[1] Department of Dermatology, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-0012, Japan
[2] Department of Dermatology, Rinku General Medical Center, Japan

Reprints: T. Ikeda
Fax: (+81) 73 448 1908
<t-ikeda@wakayama-med.ac.jp>

Article accepted on 19/1/2006

Endotoxin shock due to *Vibrio vulnificus* infection

A 54-year-old man with hepatitis C fell into shock with symptoms similar to enterocolitis after ingesting an undercooked barbecued mackerel. Most of his eruptions developed into annular erythema with small vesicles. He had taken high dose corticosteroids with intravenous cefotiam. His eruptions improved, but his shock state was exacerbated on Day 2. Treatment for endotoxin shock was initiated using piperacillin, intravenous immunoglobulin (IVIg), and hemoperfusion with Polymyxin B immobilized fiber (PMX-F), which resulted in shock reversal. The serum IL-6 value was 118,000 pg/mL on admission, and decreased to 2040 pg/mL on Day 3. On Day 6, the results from the culture of skin biopsy specimens showed the diagnosis as *Vibrio vulnificus* septic shock. Debridement was not needed, which is thought to be essential to *Vibrio vulnificus* sepsis. The changes in the serum IL-6 levels demonstrated that hemoperfusion with PMX-F and IVIg therapy was practical for *Vibrio vulnificus* septic shock.

Key words: corticosteroid, hemoperfusion, interleukin-6, intravenous immunoglobulin (IVIg), Polymyxin B immobilized fiber (PMX-F), *Vibrio vulnificus*

Vibrio vulnificus is a gram-negative bacterium which is found in warm seawater. *Vibrio vulnificus* infection results in 3 clinical syndromes: primary septicemia, wound infection, and gastrointestinal diseases. The conditions which predispose to *Vibrio vulnificus* are underlying diseases, particularly liver cirrhosis. The others are liver disorders except liver cirrhosis, hemochromatosis, diabetes mellitus, or immunocompromised host. Oral infection after ingesting raw marine products or wound infection in susceptible individuals such as those with chronic liver disease can induce fulminant septicemia and a fatal outcome. These syndromes have a poor prognosis: the mortality rate has been reported to range from 41% [1] in Taiwan to 69.6% [2] in Japan. We report here a surviving case of endotoxin shock due to *Vibrio vulnificus* infection.

Case report

A 54-year-old man who had been diagnosed with hepatitis C, ingested some undercooked barbecued mackerel on October 18th, 2001. About 4 hours later he had a fever, stomachache, and diarrhea. About 12 hours later erythematous skin lesions appeared on his right and left eyelids, and later on his limbs developed acute pain, so he consulted the neighboring hospital. He received corticosteroids equivalent to 1005 mg hydrocortisone with cefotiam hydrochrolide administrated intravenously, but he fell into a state of shock. He was conveyed to the intensive care unit of our hospital on October 19th.

On admission his body temperature was 38.9 °C; blood pressure 72/40 mmHg; and pulse rate 100/min. Most of the skin lesions were annular erythema with small vesicles which surrounded edematous pale maculae or purpura, whereas some lesions were only purpura *(figure 1A* and *B)*. The main laboratory findings were as follows: white blood cell count 1,400/μL, red blood cell count 365×10^4/μL, hemoglobin 12.8 g/dL, hematocrit 36.7%, platelet count 7.9×10^4/μL, prothrombin time 54.3%, fibrinogen 266 mg/dL, fibrinogen degradation product 7.3 μg/mL, C-related protein 9.86 mg/dL, sodium 136 mEq/L, potassium 3.5 mEq/L, chloride 100 mEq/L, calcium 8.1 mg/dL, inorganic phosphate 4.1 mg/dL, creatinine 2.5 mg/dL, urea nitrogen 32 mg/dL, uric acid 10.6 mg/dL, NH3 68 μg/dL, total protein 5.2 g/dL, albumin 2.8 g/dL, creatine kinase 1869 IU/L, lactate dehydrogenase 227 IU/L, glutamic oxaloacetic transaminase 94 IU/L, glutamate pyruvate transaminase 62 IU/L, amylase 51 IU/L. total bilirubin 1.0 mg/dL. At first anaphylactic shock from the mackerel with bacterial enterocolitis or necrotizing fasciitis were suspected. A skin biopsy from the erythema lesions that was rapidly frozen and stained with haematoxylin and eosin showed edematous superficial perivascular dermatitis, and was negative for an immunofluorescent study. Additional drip infusions of 500 mg methylpredonisolone and cefotiam hydrochloride were performed.

On Day 2, most of the erythematous skin lesions had discolored or disappeared, leaving purpura, and new skin lesions were not observed. However, the hypotension, leucopenia, and thrombocytopenia were exacerbated. Complicated endotoxin shock was diagnosed according to the results of the serum endotoxin value which was 293.2 pg/mL (normal range; 0-5 pg/mL). The treatment was changed to tazobactam sodium/piperacillin sodium

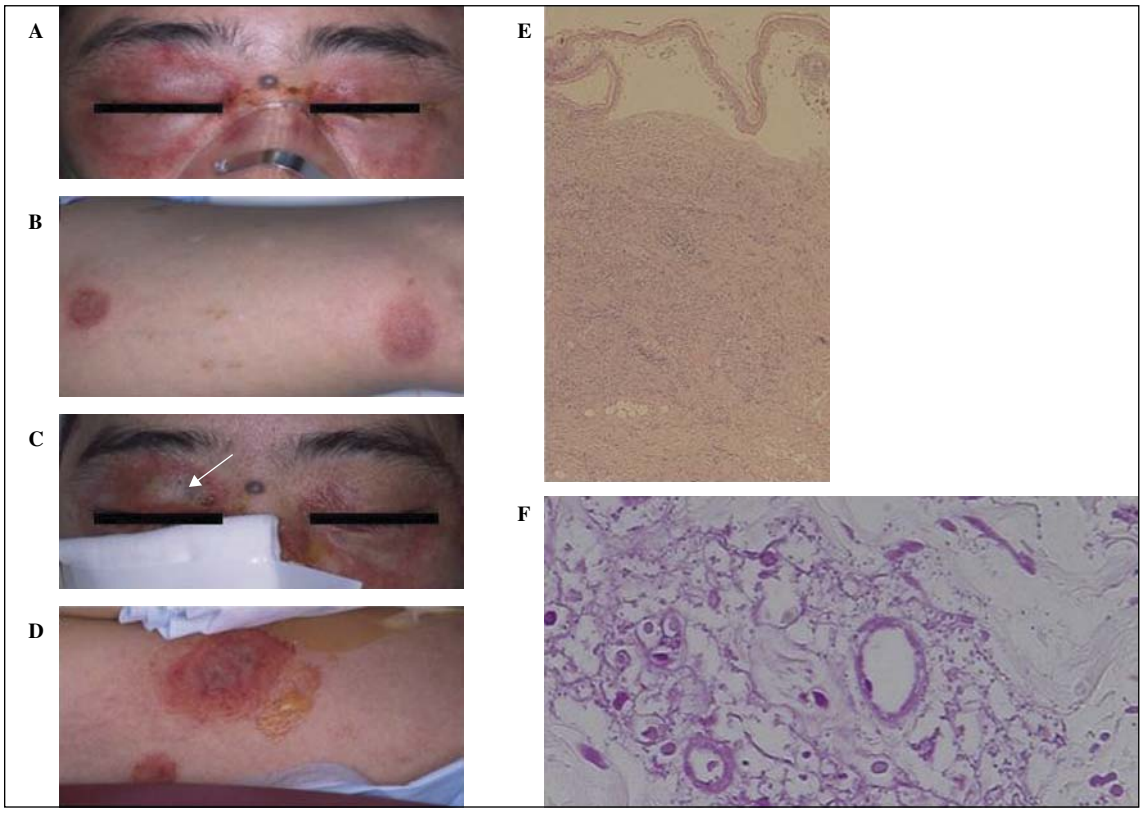

Figure 1. Annular erythema lesions surrounded edematous pale maculae or purpura on the eyelids and limbs on Day 1 **(A, B)**. The eruptions enlarged with bullous lesions leaving necrosis in the center on Days 3 and 4 **(C, D)**. The arrow shows where the skin biopsy was taken. Histopathological examinations on the purpura demonstrated subepidermal bulla, marked degeneration, and necrosis from the epidermis to the subcutaneous tissue **(E)** (Hematoxylin-Eosin stain, ×40). Structures like coccus which were negative for Giemsa stain were observed around the deep dermal vessels and degenerated collagen fibers **(F)** (Giemsa stain, ×400).

(TAZ/PIPC) drip injections in addition to intravenous immunoglobulin therapy (IVIG) and hemoperfusion with Polymyxin B immobilized fiber (PMX-F). IVIG therapy aims to supplement antibodies which bind to and neutralize toxin and opsonize bacterial cells. Polymyxin B can bind to and neutralize lipid A which is the active center of endotoxin. PMX-F is the column for hemoperfusion which is immobilized polymyxin B. Hemoperfusion with PMX-F can eliminates endotoxin from the circulation to treat septic patients. Both therapies are used for severe endotoxin shock and sepsis.

The eruptions enlarged with hemorrhagic bullous lesions, and the centers of these lesions underwent necrosis. Moreover, the erythematous lesions which had withdrawn relapsed, and multiple new erythematous or bullous lesions were identified on Days 3 *(figure 1C* and *D)* and 4. On Day 4, the results of skin biopsies taken from the center of the lesions on Day 2 and from purpura with blisters on the eyelids on Day 4 revealed that the epidermis, dermis, and subcutaneous tissue had undergone necrosis, and structures like the coccus, which were gram-negative, were seen around the dermal vessels and on the degenerated collagen fibers *(figure 1E* and *F)*.

After Day 5, most of the erythemotous lesions disappeared, leaving pigmentations, erosions, or ulcers accompanied by a decline of the serum CK and CRP values. On Day 6, a culture of the biopsied specimen from the purpura on Day 4 revealed *Vibrio vulnificus*. Since the serum CRP value had declined significantly and the severity of the eruptions was not as bad, the antibiotics were not changed *(figure 2A)*. There were no lesions which needed to be debrided.

Since the serum CK values normalized, the thrombocytopenia improved gradually, and the ulcers reduced or healed, he was discharged 1 month after admission. After his discharge he was also diagnosed with liver cirrhosis.

We measured the proinflammatory cytokines (serum tumor necrosis factor (TNF) and interleukin-1β (IL-1β)) levels by ELISA and interleukin-6 (IL-6) levels by chemiluminescent enzyme immunoassay by SRL, Inc. on admission through to Day 3 and again 1 month after the discharge. The serum TNF levels were less than normal at all times (standard value: less than 5.0 pg/mL). The IL-1β level on admission was 49 pg/ml (standard value: less than 10.0 pg/mL), but the others were negative. The serum IL-6 values were as follows: 118,000 pg/mL on admission; 26,100 pg/mL and 7,780 pg/ml on Day 2 before and after the first hemoperfusion; 2,280 pg/mL and 2040 pg/ml on Day 3 before and after the second hemoperfusion; and 2.5 pg/mL at 1 month after his discharge (standard value: less than 4.0 pg/mL) *(figure 2B)*.

Discussion

Several meta-analyses have showed that a short course of high dose corticosteroid therapy for the suppression of radical septic inflammation was ineffective in attenuating the mortality, and increased the incidence of secondary

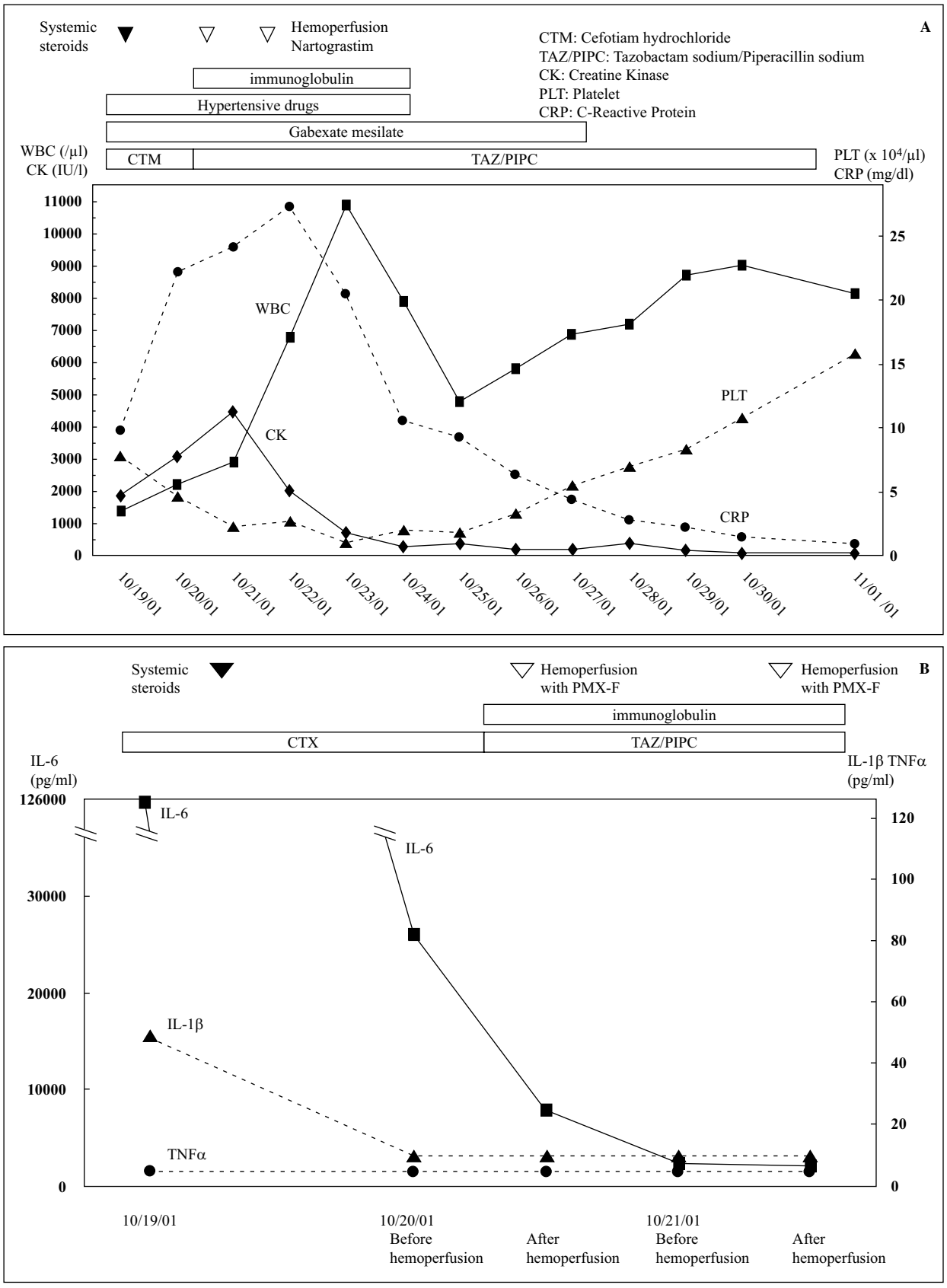

Figure 2. A) Changes in the serum WBC, creatine kinase, C-reactive protein, and pletelet values and the effects of the treatments. **B)** Changes in the serum interleukin-6, interleukin-1β, and tumor necrosis factor values (normal values; interleukin-6: less than 4.0 pg/mL, interleukin-1β: less than 10.0 pg/mL, tumor necrosis factor: less than 5.0 pg/mL).

infections [3, 4]. Recently, however, other meta-analyses reported that a long course of low dose corticosteroid therapy to improve the adrenal insufficiency due to septic shock reduced mortality [5] and improved the shock reversal [6]. This recommended therapy contains 200-300 mg/day of intravenous hydrocortisone for 7 days [7], and clinical trials have demonstrated that the initiation of both treatments within 8 hours [8] and even after 48 hours [9] from the onset of septic shock were effective. Intraveneous corticosteroid therapy equivalent to 3,505 mg of hydrocortisone was started on Day 1 according to the suspicion of anaphylactic shock. On Day 2, although his shock state deteriorated, the surrounding erythema discolored and new lesions did not appear, and debridement was not needed until discharge. Even though early comprehensive debridement has been traditionally thought to be essential, systemic corticosteroid therapy may be effective in preventing the enlargement of the erythematosus or necrotic lesions.

It is known that endotoxins induce the production of excessive cytokines such as tumor necrosis factor α, IL-1, and IL-6, which aggravate sepsis and cause endotoxin shock. Because polymyxin B can bind to and neutralize lipid A, which is the active center of endotoxin, hemoperfusion using PMX-F can eliminate endotoxins from the circulation to treat septic patients [10] and result in interrupting the progression of the inflammatory cytokine cascades. This treatment can prevent the progression to multiple organ dysfunction, and increase the survival rate by improving the hemodynamic parameters and respiratory insufficiency [11-13]. In our case after two hemoperfusion sessions, the serum endotoxin value decreased from 293.5 pg/mL to 30.2 pg/mL. The serum CK and CRP levels decreased remarkably after the first and second hemoperfusion sessions, and resolution of the septic shock was observed earlier. Therefore for endotoxin shock due to *Vibrio vulnificus* infection hemoperfusion using PMX-F was a practical treatment.

Combination treatments with doxycyclin and ceftazidime [14] or with cefotaxime and minocycline [15] are recommended as the antibiotics for severe *Vibrio vulnificus* infection. After *Vibrio vulnificus* was reported to be the pathogen, TAZ/PIPC drip injections were administrated daily because his serum CRP values continued to decrease and that showed that PIPC was effective against this strain. However Oonaka [16] *et al.* showed that there were some strains from clinical isolates which were resistant to both cefotaxime and PIPC, whereas minocycline, ciprofloxacin, and doxycycline were effective [14, 16]. Many antibiotics are nevertheless effective against this bacterium, penicillin and cephem antibiotics should be used according to the results of these susceptibility tests.

The pathogenicity of *Vibrio vulnificus* results from its capsular polysaccharide, cytolysin, lipopolysaccharide and so on. The radical release of proinflammatory cytokines induced by these substances plays a pivotal role and results in the harmful systemic effects. The serum TNF and IL-1β values in septic shock patients demonstrated a transient peak level at the onset and a rapid decline to undetectable levels. In contrast the serum IL-6 value was abnormally high during septic shock [17]. The serum level of IL-6 has also been reported to increase significantly in *Vibrio vulnificus* septicemia patients [18]. The peak IL-6 levels in septic shock were correlated with the severity of the illness, duration of survival, and the peak TNF levels [17, 19]. The IL-6 peak level during septic shock was also significantly higher in non-survivors and patients with an acute onset [19, 20].

It has been documented that after doxycycline treatment, the serum TNF and IL-1β levels of septic patients due to *Vibrio vulnificus* infection decreased significantly as compared to before the treatment, whereas the serum IL-6 level did not change [18]. However, penicillin with a β-lactamase inhibitor and cefems are known to have no effect on IL-1, -6, and TNF levels. Low dose corticosteroid therapy for septic shock attenuated the inflammatory responses due to the decreased serum IL-6 and -8 levels [21] without immunosuppression [22], although high dose corticosteroid therapy is not known to influence the cytokine profiles. The serum TNF and IL-6 values have been reported to decrease in survival patients after hemoperfusion using PMX-F [23, 24]. In addition, IVIg was indicated a possible cause for the decline in IL-6 [25] levels. This change in serum IL-6 level showed that hemoperfusion using PMX-F or IVIg therapy was also useful for modulating radical proinflammatory cytokines.

In conclusion we experienced a survival case of *Vibrio vulnificus* endotoxin shock treated with antibiotics, hemoperfusion, and immunoglobulin therapies. This case did not receive any debridement. Although high dose corticosteroid therapy has been reported to be ineffective or harmful, systemic corticosteroids may resist the expansion of cutaneous lesions due to *Vibrio vulnificus* primary septicemia. ■

Acknowledgements. *This work was supported in part by a Segawa Skin Research Grant.*

References

1. Hsueh PR, Lin CY, Tang HJ, *et al. Vibrio vulnificus* in Taiwan. *Em Infect Dis* 2004; 10: 1363-8.
2. Kojo Y, Johno M, Nakagawa K, Ono T. *Vibrio vulnificus* infection: Strategy for diagnosis and treatment. *Jpn J Dermatol* 1999; 109: 875-84; (in Japanese).
3. Lefering R, Neugebauer EA. Steroid controversy in sepsis and septic shock: A meta-analysis. *Crit Care Med* 1995; 23: 1294-303.
4. Cronin L, Cook DJ, Carlet J, *et al.* Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med* 1995; 23: 1430-9.
5. Annane D, Bellissant E, Bollaert PE, *et al.* Corticosteroids for severe sepsis and septic shock: a systemic review and meta-analysis. *BMJ* 2004; 329: 480.
6. Minneci PC, Katherine JD, Banks SM, *et al.* Meta-analysis: The effect of steroids on survival and shock during sepsis depends on the dose. *Ann Intern Med* 2004; 141: 47-56.
7. Keh D, Sprung CL. Use of corticosteroid therapy in patients with sepsis and septic shock: An evidence-based review. *Crit Care Med* 2004; 32: S527-S533.
8. Annane D, Sébille V, Charpentier C, *et al.* Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288: 862-71.
9. Bollaert PE, Charpentier C, Levy B, *et al.* Reversal of late septic shock with supraphysiolosic doses of hydrocortisone. *Crit Care Med* 1998; 26: 645-50.
10. Kodama M, Tani T, Hasegawa K, *et al.* Treatment of sepsis by plasma endotoxin removal: hemoperfusion using a polymyxin-B immobilized column. *J Endotoxin Res* 1997; 4: 293-300.
11. Sato T, Tadakuma N, Ikezaki N, *et al.* Endotoxin removal column containing polymyxin B immobilized fiber is useful for the treatment of the patient with *Vibrio vulnificus* septicemia. *Artif Organs* 1998; 22: 705-7.

12. Sato T, Shoji H, Koga N. Endotoxin absorption by polymyxin B immobilized fiber column in patients with systemic inflammatory response syndrome: The Japanese experience. *Ther Apher and Dial* 2003; 7: 252-8.
13. Tani T, Hasegawa K, Endo Y, *et al.* Therapeutic apheresis for septic patients with organ dysfunction: Hemoperfusion using a polymyxin B immobilized column. *Artif Organs* 1998; 22: 1038-44.
14. Chiang SR, Chuang YC. *Vibrio vulnificus* infection: clinical manifestations, pathogenesis, and antimicrobial therapy. *J Microbiol Immunol Infect* 2003; 36: 81-8.
15. Chuang YC, Ko WC, Wang ST, *et al.* Minocyclineand cefotaxime in the treatment of experimental murine *Vibrio vulnificus* infection. *Antimicrob Agents Chemother* 1998; 42: 1319-22.
16. Oonaka K, Furuhata K, Kikuchi A, *et al.* A basic study of Vibrio vulnificus infection: Serotyping and drug sensitivity test of environment-derived strains and human clinical isorates. *Kansenshogaku Zasshi* 2004; 78: 83-9; (in Japanese).
17. Damas P, Ledoux D, Nys M, *et al.* Cytokine serum level during severe sepsis in human IL-6 as a marker of severity. *Ann Surg* 1992; 215: 356-62.
18. Shin SH, Shin DH, Ryu PY, *et al.* Proinflammatory cytokine profile in *Vibrio vulnificus* septicemic patients' sera. *FEMS Immunol Med Microbiol* 2002; 33: 133-8.
19. Calandra T, Gerain J, Heumann D, *et al.* High circulating levels of interleukin-6 in patients with septic shock: Evolution during sepsis, prognostic value, and interplay with other cytokines. *Am J Med* 1991; 91: 23-9.
20. Damas P, Canivet JL, Groote DD, *et al.* Sepsis and serum cytokine concentrations. *Crit Care Med* 1997; 25: 405-12.
21. Briegel J, Jochum M, Gippner-Steppert C, Thiel M. Immunomodulation in septic shock: Hydrocortisone differentially regulates cytokine responses. *J Am Soc Nephrol* 2001; 12: S70-S74.
22. Keh D, Boehnke T, Weber-Cartens S, *et al.* Immunologic and hemodynamic effects of "low dose" hydrocortisone in septic shock. A double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med* 2003; 167: 512-20.
23. Tani T, Hasegawa K, Kodama M, *et al.* Correlation between plasma endotoxin, plasma cytokines, and plasminogen activator inhibitor-1 in septic patients. *World J Surg* 2001; 25: 660-8.
24. Ikeda T, Ikeda K, Nagura M, *et al.* Clinical evaluation of PMX-DHP for hypercytokinemia caused by septic multiple organ failure. *Ther Apher and Dial* 2004; 8: 293-8.
25. Suzuki H, Ikeda T, Ikeda K. Changes in various cytokines and mediators by the administration of IVIg in sepsis patients. *ICU&CCU* 2004; 28: 119-24; (in Japanese).