Endotoxin adsorption treatment for septic shock

Effectiveness, indications and initiation timing

Septic shock, which can lead to multiple organ failure, results from an overwhelming production of various kinds of inflammatory cytokines, coagulation-fibrinolysis factors, and cellular adhesion factors through systemic inflammation due to sepsis. Endotoxin is one of the causative substances of sepsis. Direct hemoperfusion (DHP) with an immobilized polymyxin B fiber cartridge (Toraymyxin™, Toray Industries, Inc., Tokyo, Japan) adsorbs and eliminates circulating blood endotoxin, and effectively improves hemodynamics and respiratory functions. Two experts in emergency medicine, Dr. Seishiro Marukawa, Iseikai Hospital, and Dr. Makoto Kobayashi, Tajima Emergency and Critical Care Medical Center, discussed the effectiveness of Toramyxin to treat septic shock, indications for treatment, and the initiation timing to apply the treatment.

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Comments

Makoto Kobayashi, MD, PhD

We conducted a study targeting patients who developed septic shock after emergency surgery for abdominal infection, and found that Toraymyxin not only significantly improved the hemodynamics and respiratory functions of patients, but also significantly shortened ICU length of stay, as compared with patients who were not treated with Toraymyxin.

Until now, the effects of Toraymyxin have been believed to be attributed largely to the adsorption and removal of endotoxin. However, recent studies have shown that the adsorption and removal of other mediators, such as endogenous cannabinoids released from monocytes, macrophages and platelets in the early stage of endotoxin shock, suppress inflammatory cytokines as well as HMGB-1, the "mediator of death," produced and released during the later stage.

Patients with septic shock and septic multiple organ failure are extremely difficult to treat. I believe that Toraymyxin is currently one of the most effective treatment methods available.

I am convinced that the strategy to use Early Goal-Directed Therapy with Toraymyxin is essential. According to this strategy, the physician firstly should confirm that septic shock is not improving despite the treatment of infectious focus, sufficient intravenous fluid infusion and administration of catecholamine, and then should treat the patient with Toraymyxin without delay.

Seishiro Marukawa, MD, PhD

Although not applicable to all patients, some can recover from septic shock if they are treated with Toraymyxin. I strongly hope that as many septic shock patients as possible can benefit from Toraymyxin by the physician's accurate assessment of its indications for treatment. For this purpose, we should not forget the key principle of clinical medicine—to diagnose septic shock as early as possible, and immediately begin treating the infection that is causing sepsis.

I believe that the greatest obligation of physicians practicing emergency and intensive care is to save as many lives as possible. They should diagnose sepsis as early as possible, and if they judge that they cannot provide adequate treatment at their facilities, they should transfer their patients to an emergency and intensive care facility specializing in septic shock.

We are using Toraymyxin as early as possible. Standard practice for using Toraymyxin was only after catecholamine had been fully administered. However, in many specialized institutions, Toraymyxin treatments are now started concurrently with the catecholamine administration. Patients treated with Toraymyxin early, recover from septic shock more easily than those who are not treated early enough. Toraymyxin appears to be one of the most effective treatments for improving blood pressure in septic shock.

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Effectiveness of Toraymyxin against septic shock

Recently, new treatments for septic shock are often evaluated by an improvement in survival rate or rehabilitation rate after hospital discharge of patients, rather than by an improvement in the clinical condition of patients after the treatment. Dr. Kobayashi has carried out a study targeting the patients who developed septic shock after the emergency surgery for abdominal infection. He found that hemodynamics and pulmonary oxygenation capabilities improved sooner, resulting in an earlier discharge from the ICU, in the Toraymyxn treated group versus the untreated group.

Marukawa: Toraymyxin is a hemoperfusion device for treating endotoxemia and endotoxic shock by adsorbing endotoxin as the causative substance. Low blood pressure is a characteristic aspect for endotoxin shock, and if Toraymyxin treatment for the shock results in an increase in blood pressure we can conclude that the treatment was effective. However, the criteria for assessing clinical outcomes have recently been changed, and indicators for measuring clinical outcomes of Toraymyxin treatment are mortality and rehabilitation rate of the patient after discharge from the hospital.

As one of the indicators for assessing therapeutic effects, you have reported "ICU length of stay" as an endpoint. This can be clearly interpreted as an "ability for patients to return to work," so I think we could admit your findings as meaningful.

Kobayashi: Patients with septic shock were assigned to either the standard treatment with Toraymyxin (Toraymyxin group) or standard treatment without Toraymyxin (Control group). I performed the study adopting the same criteria such as indications, initiation timing of Toraymyxin and withdrawing from the ICU (**Fig. 1**).

The MAP/CAI* (indicator of hemodynamics) and PaO_2/F_IO_2 ratio (indicator of pulmonary oxygenation) significantly improved in the Toraymyxin group. SOFA scores (assessment for sepsis-related, multiple organ failure) rapidly improved. I believe Toraymyxin can accelerate the improvement of systemic condition and these outcomes led to an earlier discharge of patients from the ICU.

Marukawa: Did their prognosis improve?

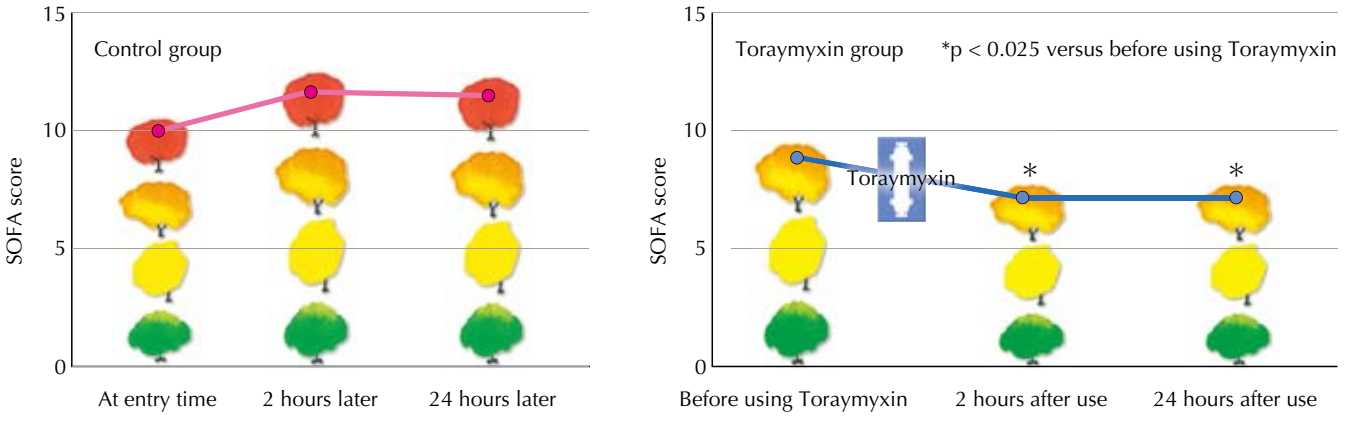
Kobayashi: Twenty-eight–day survival rates were 67% in the Toraymyxin group, and 47% in the Control group. We must keep in mind that hemoperfusion is supportive care and is not used for the purpose of source control. To be honest, I feel reluctant to compare survival rates between these two groups. It is similar to discussing survival rates in relation to interventions such as mechanical ventilation or intravenous hyperalimentation.

Marukawa: I agree. I feel slightly uncomfortable to assess all of medical treatments in terms of life prognosis, especially in terms of the rehabilitation rate of the patients returning to their work. However, we should follow the current evaluation methods for assessing the therapeutic effect.

On another point, your study targeted patients with abdominal sepsis. You must have found that evaluating them as a group correctly was complex since sepsis differs drastically from patient to patient. Besides the difficulties of choosing a homogeneous patient population, you are required to assess patient outcomes from the survival rate.

* MAP/CAI: (Mean arterial pressure) ÷ (Catecholamine Index**)
** Catecholamine Index = Dopamine (μg/kg/min) + Dobutamine (μg/kg/min) + Noradrenaline (μg/kg/min) × 100

Fig. 1-1. SOFA scores drop with Toraymyxin therapy



A pilot controlled study targeted 44 patients admitted to one of three medical institutions. Targeted population was sepsis-induced hypotensive patients even after radical surgical operation due to abdominal infections regardless of gram-negative or gram-positive infection. Twenty-five patients received Toraymyxin treatment (Toraymyxin group) and 19 did not (Control group).

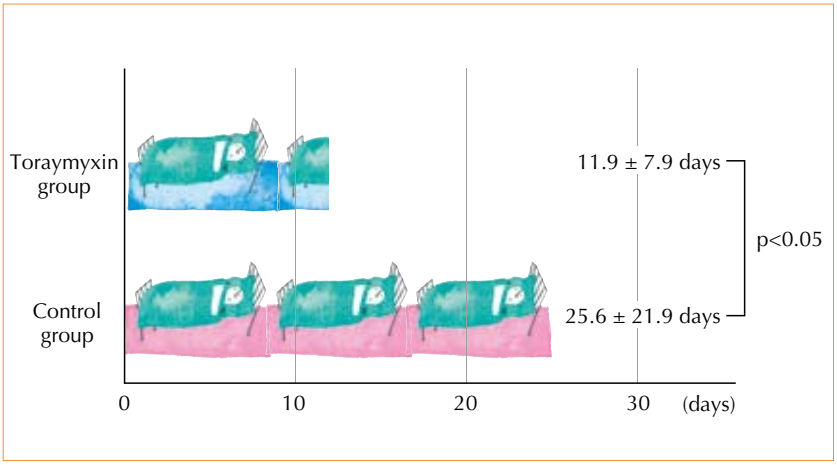
During Toraymyxin treatment, blood flow rate was 80 mL/min for 2 hours through direct hemoperfusion.

Optimal coagulation time was set between 150 and 200 sec, with the anticoagulant dose (nafamostat mesilate) adjusted accordingly.

Patients in the Toraymyxin group had rapid improvements in their SOFA scores and spent shorter staying days in the ICU than patients in the Control group.

(Journal of the Japanese Society for Abdominal Emergency Medicine 27(1): 45-49, 2007.)

Fig. 1-2. Comparison of ICU length of stay



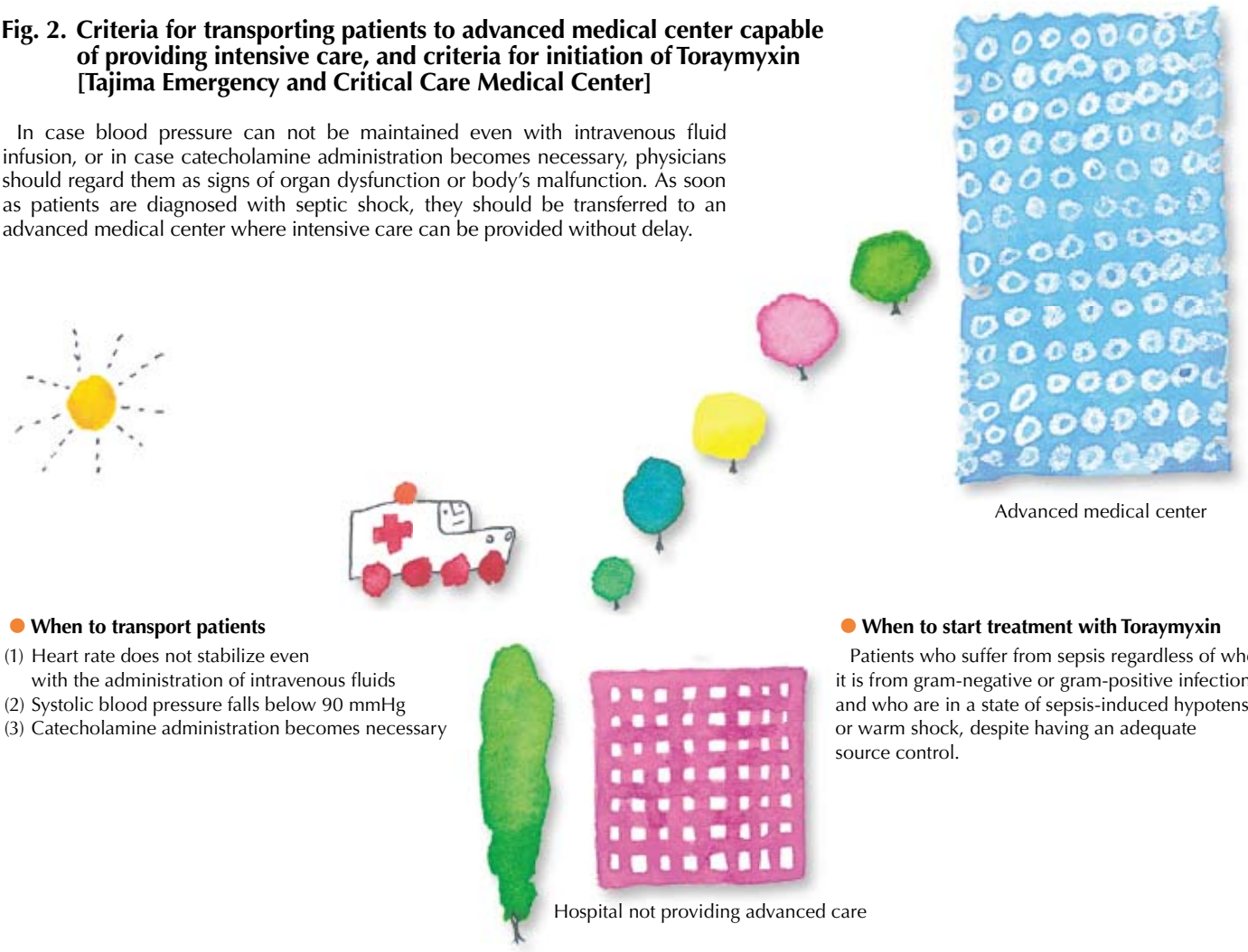
Indications for Toraymyxin therapy

Sepsis patients in "warm shock" seem to benefit more from Toraymyxin than patients in "cold shock." Therefore, we conclude that warm shock is the better indication for Toraymyxin. Medical institutions without an ICU should not wait for patients to develop organ failure before transferring them to an institution that can provide the intensive care, especially if the patients have at least one of the following: (1) unstable heart rate after intravenous (IV) infusion of fluids, (2) systolic blood pressure falling below 90 mmHg, or (3) catecholamine is required to maintain blood pressure.

Marukawa: Which patients would you recommend for treating with Toraymyxin?
Kobayashi: I'd say that appropriate patients are sepsis caused by Gram-negative or positive infection, and sepsis-induced hypotension despite radical treatment. In particular, these are patients who are in the state of "warm shock" (**Fig. 2**). On the other hand, I have the impression that patients with cold shock state do not respond well to the treatment.
Marukawa: "Warm shock" is a hyperdynamic state where the cardiac index (CI) is high and systemic vascular resistance index (SVRI) is low. I understand that warm shock is a period where the patient's condition could be compensated even with shock. Do you have any other criteria?
Kobayashi: In my study, survivors were treated with Toraymyxin within 10 hours after the onset of septic shock, while non-survivors were treated after 25 hours on average. Treatment was most often delayed because the medical facility did not have the expertise or proper equipment, and those in charge did not adequately assess the patient's condition and order an immediate transfer to a medical center that could provide the care.
Marukawa: I can see that it's important to avoid losing precious time in treating patients. What's your advice to prevent this delay of the treatment?
Kobayashi: Patients with septic shock should be immediately transferred to an advanced medical center that can provide intensive care if they have at least one of the following: (1) unstable heart rate even after IV infusion of fluids, (2) decreasing systolic blood pressure below 90 mmHg, and (3) requirement of catecholamine for maintaining of the blood pressure (**Fig. 2**).
Marukawa: I know that, even with septic shock, doctors tend to be reassured if patients can still urinate, or if their respiratory failure doesn't deteriorate, and come to regard the situation as not serious enough to warrant immediate action. It's been about twenty years since the new concept of organ failure was introduced to Japan. However, the diagnostic criteria for organ failure tended to be interpreted as criteria for initiating treatment. As you have just mentioned, if blood pressure cannot be maintained even with intravenous fluid infusion, or if catecholamine administration becomes necessary, I believe that physicians should regard them as signs of organ dysfunction or body's malfunction.
Kobayashi: I fully agree with you. Soon after the physician diagnoses warm shock, he or she should immediately decide which treatment is best for the patient.

Fig. 2. Criteria for transporting patients to advanced medical center capable of providing intensive care, and criteria for initiation of Toraymyxin [Tajima Emergency and Critical Care Medical Center]

In case blood pressure can not be maintained even with intravenous fluid infusion, or in case catecholamine administration becomes necessary, physicians should regard them as signs of organ dysfunction or body's malfunction. As soon as patients are diagnosed with septic shock, they should be transferred to an advanced medical center where intensive care can be provided without delay.



● When to transport patients

(1) Heart rate does not stabilize even with the administration of intravenous fluids
(2) Systolic blood pressure falls below 90 mmHg
(3) Catecholamine administration becomes necessary

● When to start treatment with Toraymyxin

Patients who suffer from sepsis regardless of whether it is from gram-negative or gram-positive infection and who are in a state of sepsis-induced hypotension or warm shock, despite having an adequate source control.

Toraymyxin: Treatment Initiation Timing

Toraymyxin is indicated for patients whose respiratory and hemodynamic functions have not improved, even after antibiotic treatment, IV infusion of fluids or catecholamine. As a basic rule, the physicians in emergency care recommend a strategy of Early Goal-Directed Therapy (EGDT) using Toraymyxin.

Kobayashi: I believe that therapeutic effects can be expected if radical treatment is provided from the onset of shock and if Toraymyxin is administered as soon as possible. We follow a modified EGDT protocol that includes Toraymyxin. (**Fig. 3**)
Marukawa: What is your goal for the improvement of hypovolemia, which is one of the therapeutic target?
Kobayashi: The central venous pressure (CVP) level used to be set at 8 mmHg, but in the case of abdominal infections, we administer intravenous fluids at up to 12 mmHg. When we evaluate the CVP of patients with mechanical ventilation, we can't obtain the precise data because positive end-expiratory pressure (PEEP) influences the value of CVP. So we use an echocardiogram to measure the diameter of left ventricular dilatation and central veins for the evaluation.
Marukawa: How is catecholamine used?
Kobayashi: As a first-line drug, we use from 5 μg/kg/min to 15 μg/kg/min of dopamine, and then administer noradrenalin concomitantly at up to 0.1 μg/kg/min. If blood pressure still does not increase, then we consider using Toraymyxin.
Marukawa: Would you recommend measuring CVP and using an echocardiogram in this manner, not only to experts of the ICU and emergency department, but also to other clinicians?
Kobayashi: I suppose some doctors might find it troublesome to evaluate hypovolemia with an echocardiogram. Instead, I suggest using Toraymyxin in the following situations:

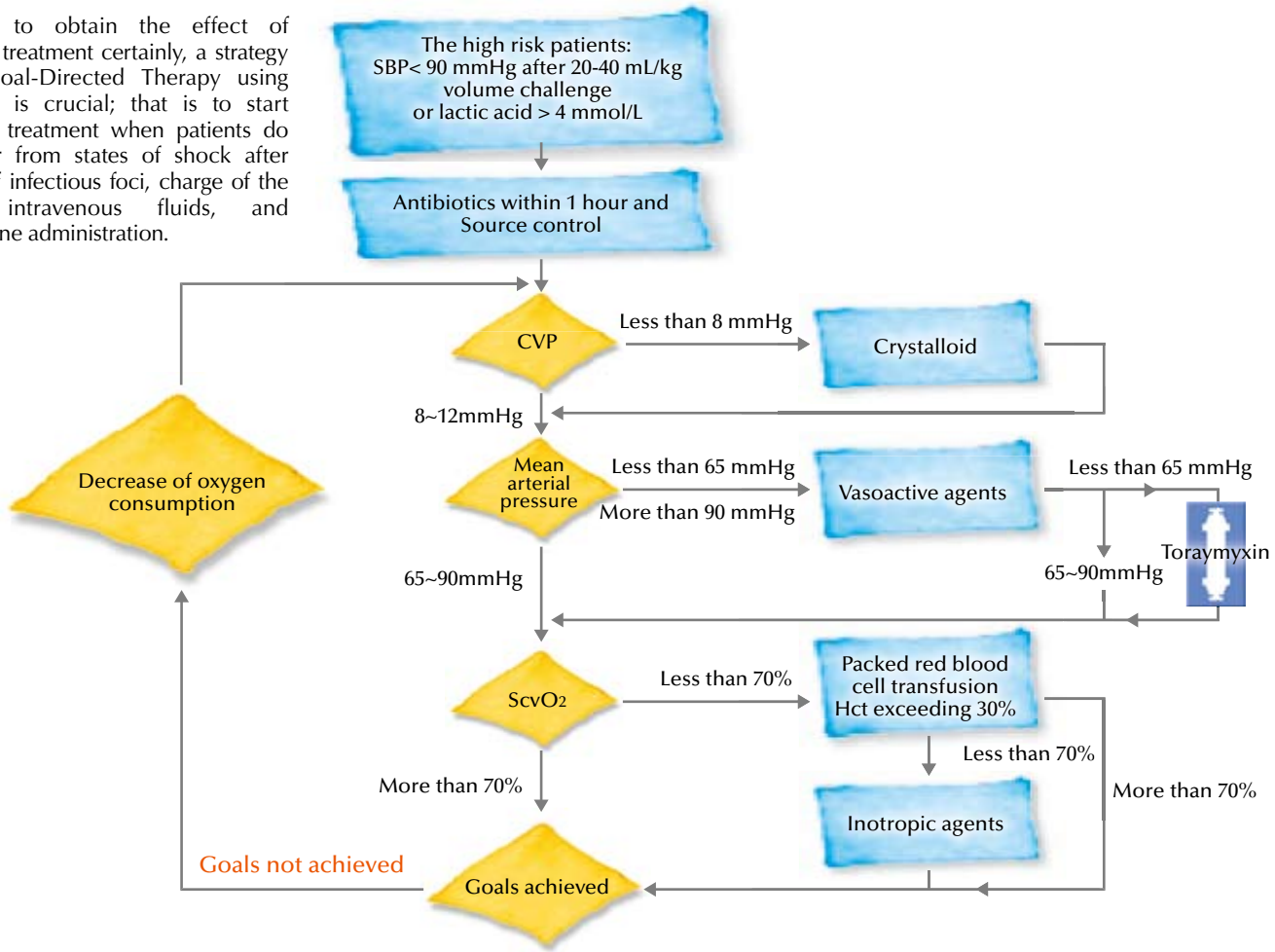
1. CVP is over 8 mmHg
2. Catecholamine (with more than 5 μg /kg/min of dopamine) is required to maintain systolic pressure over 90 mmHg

Marukawa: Can you suggest any other strategies, such as easing the criteria for applying Toraymyxin?
Kobayashi: I have performed clinical evaluations for many years, and find that the number of patients that I am treating with Toraymyxin has been decreasing each year. I prescribe the Toraymyxin treatment for each patient based on my experience, such as "I may have missed the appropriate timing for using Toraymyxin on this patient," or "This patient can improve without Toraymyxin."
Marukawa: I guess you can say that the more experience a clinician accumulates, the more conservative or "slimmer" his or her treatment becomes. The relationship between the medical condition and mechanism of action that makes Toraymyxin effective remains unclear; and there may be other diseases for which Toraymyxin would work, as you have shown with idiopathic pulmonary fibrosis.

My last question is, "Do you think that we need to define the indications for Toraymyxin and the initiation of treatment?"
Kobayashi: Yes.
Marukawa: So, our conclusion is that we should treat patients based on verification, as you have shown.

Fig. 3. Strategy of Early Goal-Directed Therapy using Toraymyxin

In order to obtain the effect of Toraymyxin treatment certainly, a strategy of Early Goal-Directed Therapy using Toryamyxin is crucial; that is to start Toraymyxin treatment when patients do not recover from states of shock after treatment of infectious foci, charge of the sufficient intravenous fluids, and catecholamine administration.



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