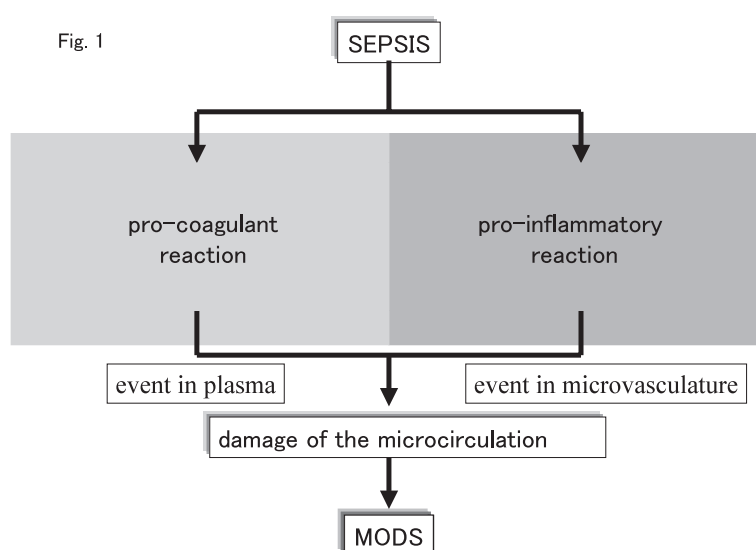


The anti-coagulant therapy for septic organ dysfunction

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It is widely accepted that the activation of coagulation plays the major role in the development of organ dysfunction during sepsis. The observation under the intravital microscopy have revealed that the damage of vascular endothelium and micro-thrombus formation resulting in the disturbance of microcirculation (Fig. 1).



Based on this theory, the efficacy of treatment with anticoagulants for severe sepsis has been examined in clinical trials. Recombinant human activated protein C (rhAPC) became the first drug approved by the Food and Drug Administration (FDA) for the treatment of severe sepsis in the United States. Following the online announcement of success of the rhAPC trial in 2001 in the New England Journal of Medicine (PROWESS trial),

the results of two other trials using natural anticoagulants were published: The KyberSept trial (high-dose antithrombin (AT) in patients with severe sepsis) and the OPTIMIST trial (recombinant tissue factor pathway inhibitor (rTFPI) in patients with severe sepsis). While AT and recombinant TFPI did not show a survival benefit in patients with sepsis, rhAPC did (Table1).

agents (trial)	recombinant APC (PROWESS trial)	antithrombin III (KyberSept trial)	recombinant TFPI (OPTIMIST trial)
shock/total case	1200/1690 (71.0%)	1118/2314 (48.3%)	1301/1987 (65.5 %)
mortality in treatment: placebo	30.8% : 24.7% P= 0.005	38.4% : 38.9% N.S.	34.2% : 33.9% N.S.
Relative Risk (95% CI) in total	0.80 (0.69-0.94)	1.01 (0.91-1.11)	1.01 (0.89-1.15)
Relative Risk (95% CI) in shock	0.82 (0.71-0.95)	1.01 (0.88-1.15)	0.96 (0.72-1.28)
conclusion	effective	efficacy was not recognized	efficacy was not recognized

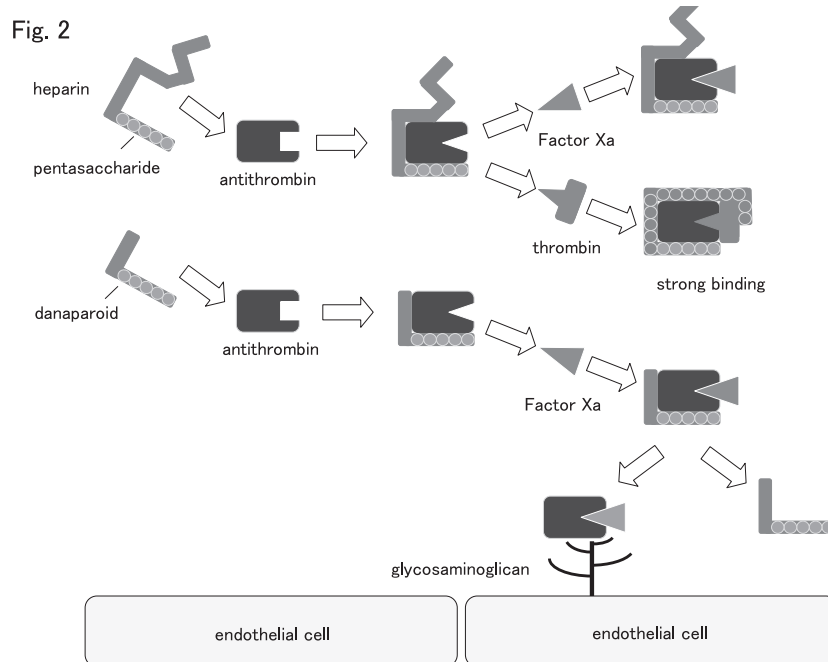
Table1. Comparison of three clinical trials for severe sepsis

However, “does absence of proof of efficacy provide proof of the absence of efficacy?”. Since each of these trials enrolled nearly 2,000 subjects (OPTIMIST trial) or more (KyberSept trial), we should learn more about sepsis treatment from these trials. In this seminar, we raise the following questions:

- Does the improvement of hypercoagulopathy improve the survival?
- Was the severity of sepsis of the subjects enrolled different?
- Was the timing of treatment appropriate?
- Was the dose of agents sufficient?
- Did concomitant heparin abolish the anti-inflammatory effects?

- Did administration of concomitant heparin increase the adverse events?
- How presents the next future study in this indication?

For the last question, we introduce our unique approach using danaparoid sodium (DS). DS is a low-molecular-weight heparinoid with a mean molecular weight of approximately 6000 Dalton. It consists mainly of heparan sulfate and dermatan sulfate. The high-affinity fraction of the heparan sulfate inhibits factor Xa by catalyzing its binding to AT. Compared to unfractionated heparin, DS has a lower binding affinity for AT and shift the antithrombotic activity from thrombin to factor Xa (Fig. 2).



Thus, AT/DS combination therapy offers less bleeding and more significant anti-inflammatory effects. Currently, these beneficial effects have been investigated in an animal model in our laboratory.