National Consensus on the Management of Disseminated Intravascular Coagulation in Sepsis 2001

Association of Intensive Care Physicians of Indonesia
Indonesian Shock Society
Indonesian Society on Thrombosis and Hemostasis
Working Unit for Emergency Pediatrics – Indonesian Pediatrician Association
Indonesian Society of Hematology and Blood Transfusion

INTRODUCTION

In the last two decades, knowledge on sepsis, particularly on pathophysiology and therapy, has developed immensely, even for conditions prior to clinical and laboratory manifestations of disseminated intravascular coagulation. It is also known that activation of the coagulation system may take place simultaneously with sepsis.

In the year 1991, the American College of Chest Physicians and the Society of Critical Care Medicine agreed on a definition for sepsis in order to facilitate clinicians in establishing early diagnosis and providing rapid management.[1] Nonetheless, the morbidity and mortality of sepsis remains high, one of its causes being multiple organ failure (MOF). DIC is a syndrome characterized by disseminated (as supposed to local) activation of coagulation within the vascular system due to various causes.[2] Formation of microthrombi due to activation of the coagulation process and development of DIC is a cause of MOF.

In a meeting in Semarang on the 24th to 25th of February 2001, participants representing the Association of Intensive Care Physicians of Indonesia, the Indonesian Shock Society, the Association of Thrombosis-Hemostasis of Indonesia, the Work Unit for Emergency Pediatrics – Indonesian Pediatrician Association, and the Association for Hematology and Blood Transfusion of Indonesia agreed on DIC management. This meeting did not only aim at establishing a detailed management protocol, but also to establish guidelines for individuals or institutions to formulate management protocols more suitable with local conditions.

METHODOLOGY

The method for the formulation of this consensus follows established methods for consensus formulation.[3] During the pre-consensus meeting, questions on the aspects of pathophysiology, diagnosis, and management were formulated. Participants were divided into 3 groups, each responsible for the collection of data and literature to answer each question. At the general assembly for the consensus, answers to all of the questions were formulated and discussed by all the participants.

The literature collected were mostly clinical trials,

Table 1. Reliability level of clinical studies based on grading system.[4]

Level	Grading System
I	Randomized study on large populations with a clearly significant result. The possibility of false positives or negatives is small.
II	Small randomized study with slightly significant results. Moderate to great possibility of false positives or negatives.
III	Controlled non-randomized study.
IV	Non-randomized study, with historic control or expert opinion.
V	Case series, studies without control or expert opinion.

Table 2. Answers to questions based on grading system.[4]

A	Supported by at least 2 level I studies
B	Supported by at least 1 level I study
C	Supported by level II studies
D	Supported by 1 level III study
E	Supported by level IV or V studies

and was then classified into the grading levels I to V based on evidence/reliability level (Table 1). The answers to the questions were given a recommendation based on grades A to E (Table 2). After a consensus is reached, the editorial team formulates the consensus paper, to then be distributed to all the participants for a final correction prior to publication.

DIC PATHOPHYSIOLOGY IN SEPSIS

One of the complications of sepsis is multi-organ dysfunction and bleeding due to DIC. Full blown clinical symptoms of DIC are characterized by the formation of disseminated microvascular thrombosis and bleeding in various places. The prevalence of DIC in sepsis ranges from 7.5% to 50%. Multiple organ dysfunction and mortality rates are higher in sepsis with DIC compared to those without.[5]

In sepsis, hemostasis changes vary from mild hemostasis disturbances to DIC. Changes in the hemostasis system that occur, particularly includes the role of tissue factors activation of the coagulation system, inhibition of

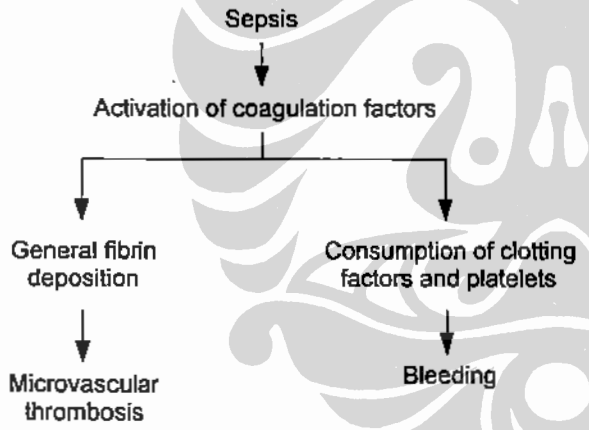

Figure 1. Pathogenesis of microvascular thrombosis and bleeding in sepsis.[6]

the coagulation-anticoagulant system, and changes in the fibrinolysis system mediated by released mediators or cytokines induced by bacterial toxins.

Current studies demonstrate a close interaction between inflammation and the coagulation system. It is known that the coagulation system can be activated by inflammation, while activation of the coagulation factor also influences the development of the inflammatory process in sepsis.

Developments in the knowledge on the pathophysiology of sepsis, particularly current knowledge on the pathophysiology of coagulation disorder during sepsis,

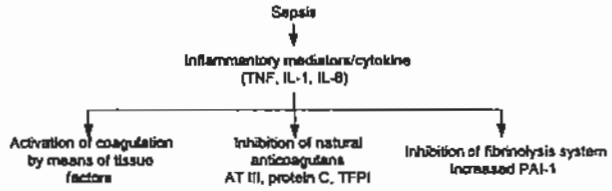

Figure 2. Scheme of coagulation disorder in sepsis.[7]

have clinical implications in the management of sepsis. Several studies on medications such as AT III and C protein have been conducted, and is hoped to reduce the mortality rate in sepsis.

DISSEMINATED INTRAVASCULAR COAGULATION IN SEPSIS.[8-9]

General fibrin deposition due to activation of coagulation during sepsis causes formation of thrombi in the blood vessels, particularly in small and medium blood vessels, causing microvascular thrombosis, and subsequent multi-organ dysfunction. The coagulation process that occurs since the beginning of sepsis continues, resulting in the consumption of coagulation factors and platelets. Consumption of coagulation factors and platelets causes deficiency and bleeding (Figure 1).

SEPSIS

Activation of the coagulation system, inhibition of the natural anticoagulant and fibrinolysis system.[6-13]

Inflammatory mediators such as tumor necrosis factor (TNF), interleukin 1 (IL-1), and interleukin 6 (IL-6) cause the activation of coagulation factors, particularly through tissue factors, inhibition of the natural anticoagulant pathways, and inhibition of fibrinolysis through increased inhibition of plasminogen activator inhibitors type 1 (PAI-1). These conditions cause increased fibrin formation and loss of the ability to perform fibrin degradation.

During sepsis, coagulation factors may be activated through intrinsic and extrinsic pathways. Due to very low levels of factor XII (Hageman factor) in patients with sepsis, the intrinsic pathway is thought to play a role in the activation of coagulation factors. The latest studies demonstrate that the extrinsic pathway plays the main role in the activation of the coagulation factor in sepsis.[2-9] This process depends on the availability of tissue factors. Tissue factors bind factor VIIa in the formation of the tissue factor-factor VIIa complex, which then changes factor X into factor Xa, and factor IX into factor IXa. (Figure 3).

The coagulation system has several inhibitory sustems and an important role in sepsis. In sepsis, there is reduced activity of the inhibitory or anticoagulant system. Some of these anticoagulants, including antithrombin III (AT III), C protein, S protein, and other tissue factor pathway inhibitors (TFPIs). Antithrombin III acts by inhibiting thrombin and other coagulation factors (IIa, IXa, XIa, and XIIa), and also has anti-inflammatory effects. The C protein activated by the thrombin-thrombomoduline complex inactivates factor Va, VIIIa, and PAI-1, suspected to play a role in the inflammatory process. TFPI plays a role in inactivating factor Xa and factor VIIa-tissue factor complex.

The fibrinolytic system is a secondary process in

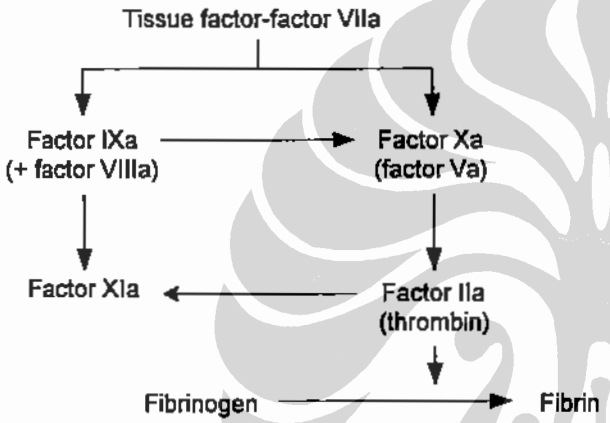

Figure 3. The scheme of the role of tissue factors in sepsis.[8]

activating the coagulation system. Study results demonstrate that the fibrinolytic system is activated proor to the inhibition. Inflammatory mediators themselves have the ability in inhibiting fibrinolysis in endothelial cells by means of stimulating the release of PAI-1. Imbalance between the coagulation system and fibrinolysis accelerates the formation of thrombi, causing organ dysfunction and subsequent mortality.

Inflammatory interactions and coagulation in sepsis.[8,13,14]

Current studies demonstrate an interaction between inflammation and coagulation in sepsis. Several coagulation factors play a proinflammatory effect, such as factor Xa and thrombin, which can increase the production of mediators of proinflammatory cytokines such as IL-6 and IL-8. On the other hand, several natural anticoagulants such as AT III and C protein play a role in anti-inflammatory process during sepsis.

These findings demonstrate that the inflammatory cascade cases and aggravates the coagulation disorder in sepsis, and vice versa the coagulation cascade also aggravates the inflammatory reaction in sepsis.

Diagnosis of Acute DIC

Question 1:

Which laboratory evaluations are required for the diagnosis of acute DIC and what do they signify?

Answer:

Laboratory evaluation for the diagnosis of DIC consists of the screening tests and determining tests, as follows:

Screening tests:

1. Platelet count
2. Prothrombine Time (PT)
3. Activated Partial Thromboplastin Time (Aptt)
4. Thrombin time
5. Fibrinogen

Determining tests:

1. Soluble fibrin monomer
2. D dimmer
3. Fibrin Degradation Product (FDP)
4. Antithrombin

A. Screening Tests:

1. Platelet count

Thrombocytopenia is found in 98% cases of DIC, 15 and 50% of DIC cases have a platelet count of less than 50,000/uL. 15, 16 According to Levi (1999), in DIC, the initial platelet count is less than 100,000/uL or rapid reduction of platelet count is found. 17 In diagnosing DIC, platelet count has a sensitivity level of 97%, but a specificity level of only 48%.[18]

2. Prothrombine Time (PT)

According to Bick (1996) prolonged prothrombin time (PT) is found in 50-70% cases of DIC. 19 Such prolongation is caused by hypofibrinoegnemia, FDP inhibiting fibrin polymeration or lysis of factors V and X by plasmin. A normal or shortened PT may be caused by the presence of active coagulation factors, or initial FDP (X and Y fragmens) rapidly frozen by thrombin. In diagnosing DIC, PT has a sensivitity rate of 91%'but a low specificity of 27%. 18 Thus, PT is generally unreliable and has minimal benefit in the diagnosis of DIC.

3. Activated Partial Thromboplastin Time (aPTT)

Prolonged activated Partial Thromboplastin Time (aPTT) is only found in 50-60% cases of DIC. The cause for prolonged aPTT is hypofibrinogenemia, FDP inhibition of fibrin polymerization, and lysis of factors V, VII, IX, and X by plasmin. The results of aPTT in DIC may be normal or shortened for the same causes as short-

ened PT. In establishing the diagnosis of DIC, aPTT has a sensitivity rate of 91%, but a specificity of only 42%.[18] As in the case of PT, aPTT is also unreliable and has minimal benefit for DIC.

4. Thrombin time

Prolonged thrombin time is caused by inhibition of fibrin polymerization by FDP and the presence of hypofibrinogenemia. This test has other benefits, because it is able to evaluate the quality of fibrinolysis. In diagnosing DIC, thrombin time has a sensitivity rate of 83% and a specificity rate of 60%.[18]

5. Fibrinogen

Evaluation of fibrinogen level does not seem to be beneficial in diagnosing DIC, since it has a sensitivity rate of only 22%, even though the specificity is 100%. Even though fibrinogen is consumed by thrombin as well as plasmin, normal fibrinogen levels does not eliminate the presence of DIC. Since fibrinogen is an acute phase protein, its levels increase under acute conditions such as sepsis. Fibrinogen levels drop after prolonged conditions.

B. Determining Test

1. Soluble Fibrin Monomer (sFM)

Soluble Fibrin Monomer (sFM) is evaluated through a paracoagulation test using prothamine sulphate or the ethanol gelation test. The presence of monomer fibrin indirectly demonstrates the presence of thrombin, thus proving coagulation activation. The sensivity and specificity rate of sFM ranges between 80-90%.[17]

2. D-dimer

D-dimer is the result of the degradation of fibrin cross linkages by plasmin, which marks coagulation activation and fibrinolysis. D-dimer is the most reliable test to confirm DIC. 17 In diagnosing DIC, D-dimer has a sensitivity rate of 91% and a specificity rate of 68%. 16 A normal D-dimer finding has a high negative predictive value for DIC.[19, 20, 21]

3. Fibrin degradation product (FDP)

FDP is the result of fibrin or fibrinogen degradation by plasmin, while this test is unable to differentiate DIC and primary fibrinolysis. Increased FDP is found in 85-100% cases of DIC. 22 FDP has a sensitivity of 100% and a specificity rate of 67%.[18]

4. Antithrombin

Antithrombin III is a coagulation inhibitor that functions by neutralizing thrombin and other serin protease such as factors Xa, IXa, XIa, and XIIa. Antithrombin III is the key test to diagnose and monitor the management of DIC. 19 In the activation of coagulation, an irreversible complex between AT III and active coagulation factors (serin protease) is formed, thus reducing AT III activity. Thus, the reduction of ATIII is due to increased consumption. In diagnosing DIC, AT III has a sensitivity rate of 91% and specificity rate of 40%.[18]

Question 2:

What are the minimal criteria for the diagnosis of DIC in sepsis?

Answer:

By studying the pathophysiology of DIC during sepsis, we can understand the disturbance in hemostasis that occurs, and almost all general hemostasis tests would turn out abnormal. Thus, we should determine which test is truly significant in establishing the diagnosis of DIC, based on reliability, specificity, and availability.

Afterwards, we should formulate the minimal criteria for the diagnosis of DIC in sepsis, the type of laboratory tests needed to diagnose DIC and indications for such testing. According to Bick (1998), the minimal clinical finding for the diagnosis of DIC in sepsis is the presence of bleeding, thrombosis, or both, in addition to sepsis.[22] We know that no single laboratory test can be used to diagnose DIC. The minimal laboratory criteria for the diagnosis of DIC in sepsis is signs of coagulation activity, evidence of fibrinolytic activation, evidence of consumption inhibition, and evidence of organ dysfunction.

To prove the presence of coagulation activation, we can examine the level of prothrombin fragments 1 and 2, throbin-antithrobin complex (TAT), soluble fibrin monomer (sFM), fibropeptide A (FPA), and D-dimer. Fibrinolytic activation can be proven by evaluating plasmin-antiplasmin (PAP), FDP, and D-dimer. To establish inhibitor consumption, we can evaluate antithrombin activity (AT), protein C or protein S, while organ dysfunction can be evaluated from ureum, creatinine, and LDH levels as well as blood gas analysis.

According to Bick, the minimal criteria for the diagnosis of DIC is simply one abnormal test result out of each category and 2 abnormal test result for organ dysfunction. Increased D-dimer can prove the presence of coagulation and fibrinolytic activation. If the reagent for D-dimer evaluation is unavailable, coagulation activation may be proven from soluble fibrin monomer evaluated from sulphate protamine or through the ethanol gelation test. FDP evaluation cannot differentiate whether plasmin degraded fibrin or fibrinogen.[22]

In the 47th conference of the International Society on Thrombosis and Haemostasis, on the 6th and 7th of July in Paris, a diagnosis criteria and scoring system for the diagnosis of DIC is formulated (Appendix 2). Evaluation is conducted based on clinical findings and routine

hemostasis evaluation. Values over 5 represent DIC, and the evaluation is repeated daily to monitor the severity of DIC.[2]

Recommendation:

The minimal criteria for the diagnosis of DIC is findings or clinical manifestations of DIC with bleeding, thromboemboli, or both, accompanied by laboratory thrombocytopenia and findings of Burr cell erythrocytes or positive D-dimer. If laboratory facilities are available, the criteria according o Bick or diagnosis based on the DIC scoring system from the 47th scientific and standardization committee of the International Society on Thrombosis and Hemostasis.

Question 3:

What is the indication of laboratory evaluation in sepsis?

Answer:

Since coagulation activation occurs in all patients with sepsis, the laboratory tests mentioned above should be conducted in all patients with sepsis to detect DIC. In addition, there is a tendency for bleeding and organ dysfunction, which are indications for laboratory evaluation for the detection of DIC.

DIC MANAGEMENT IN SEPSIS

In managing DIC, particularly that due to sepsis, the most important thing to do is treating the primary illness.[23,24,25] This includes supportive therapy (see the consensus resuscitation in patients with septic shock, 1997),[26] treatment with proper antibiotics, and elimination of the focus of infection.

DIC due to sepsis generally cannot be resolved immediately. Thus, the need for treatment to stop the intravascular coagulation process, or administration of blood components and coagulation inhibitors should be considered.[23,24,25]

As with adults, the management of pediatric patients is principally the same, with dose adjustment according to body weigh.

Question 1:

What are the indications and how should heparin be used in DIC due to sepsis?

Answer:

Up to now, there is still no agreement on the use of heparin in sepsis. Various reported case studies (without control, and with small sample populations) demonstrate contradictory results, and there is still no study demonstrating the use of heparin in reducing morbidity and mortality.[7,28-32]

Certain healthcare institutions administer heparin to try to inhibit the coagulation process, while some do not. The advantage of heparin administration is still under debate. Several conditions that make the use of heparin disadvantageous in cases of sepsis are: (1) reduced antithrombin III activity, making heparin function ineffective; (2) administration of heparin increases the risk of bleeding and thrombocytopenia. (3) Administration of heparin inhibits the release of prostacycline from endothels.

Recommendation:

Heparin is not administered in cases of DIC due to sepsis, unless there is evidence of thromboemboli. Heparin is administered as follows: 100 IU/kg bodyweight bolus followed by 15-25 IU/kg bodyweight/hour (750-1250 IU/hour) through continuous infusion, with adjusted subsequent doses to reach an aPTT of 1.5-2 times control (Grade E).

Question 2:

What are the indications and how should blood products be used in DIC due to sepsis?

Answer:

Consumption of blood coagulation factors in DIC increases the risk of bleeding. Administration of plasma and platelet concentrate is the rational treatment for DIC due to sepsis, even without clinical studies that prove the benefit of its use.

Recommendation:

Consideration on the administration of blood components is adjusted to the patient's clinical condition, and not on laboratory results alone. Transfusion of Fresh Frozen Plasma (FFP) and/or platelet concentrate is administered in cases of bleeding or risk of bleeding (prior to undergoing an invasive procedure) (Grade E).[7,32,33] In cases with very low clotting factors and platelet count (less than 30,000/mm3) consider administration of prophylactic transfusion (Grade E).

Question 3:

What are the indications and how should antithrombin III be used?

Answer:

Increased knowledge, particularly on the pathophysiology of sepsis, leads to the belief that replacement therapy, particularly administration of antithrombin III, protein C, and anti-tissue factors (TFPI) is a more rational method of therapy. Phase III clinical trials are under way.

Various clinical studies demonstrate the benefit of the use of antithrombin III in reducing the mortality rate of sepsis. Phase II clinical studies demonstrate the benefit of antithrombin III in reducing the morbidity rate of

DIC and in significantly reducing the mortality rate. 34-36 According to reports on the initial results phase III clinical studies on 2000 patients with severe sepsis, ATIII was unable to significantly reduce the mortality rate compared to control.

Recommendation:

Administration of antithrombin III is recommended as a substitute therapy if AT III activity is below 70%, with the aim of improving DIC and organ dysfunction. [25]

Antithrombin III is administerd with an initial dose of 3000 IU (50 IU/kg bodyweight) followed by 1500 IU every 8 hours through continuous infusion for 3-5 days. AT III substitution may also be administered according to the formula 1 IU x bodyweight (kg) x AT III deficiency (%), with a targer of AT III > 120% (Grade B). Use of antithrombin III concentrate together with heparin is not recommended, since it does not improve mortality rates, and instead increases the risk of bleeding. [37]

If possible, laboratory monitoring of AT III every 8 hours is recommended, or by monitoring clinical improvements (Grade E). Evaluation of the response to therapy is conducted by monitoring the DIC score.

Question 4:

What are the indications and how should anti-fibrinolytics be used?

Answer:

In cases of sepsis, no primary fibrinolysis is proven. Anti-fibrinolytics are not recommended for sepsis.

APPENDIX 2

DIC Scoring[2]

1. Risk scoring: is there a primary abnormality/etiology associated with DIC? (sepsis)
   If not, discontinue scoring.
2. Coagulation test (platelet count, PT, fibrinogen, FDP/D-dimer)
3. Score:

- Platelet count :
  > 100,000/uL = 0
  50,000-100,000/uL = 1
  < 50,000 = 2
- sFM/FDP/D-dimer
  no increase (D-dimer < 500)= 0
  moderate increase (D-dimer 500-1000)= 2
  greatly increased (D-dimer >1000)= 3
- Prolonged prothrombin time
  < 3 seconds = 0
  4-6 seconds = 1
  > 6 seconds = 2
- Fibrinogen
  < 100 mg/dl = 1
  > 100 mg/dl = 0

4. Total score
   = 5: indicates DIC, evaluation should be repeated daily
   < 5: suggestive of DIC, repeat evaluation in 1-2 days

REFERENCES

1. Bone RC, Balk RA, Cerra FB, et al. American college of chest physician/society of critical care medicine consensus conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1644-5.
2. Levi M. Conference report, disseminated intravascular coagulation: new diagnostic criteria and supportive treatment strategies, 47th scientific and standardization committee meeting of the International Society on Thrombosis and Haemostasis 2001 July 6-7: Paris, Frace. [cited 2001 Aug 19]. Available from: URL: http://www.medscape.com/Medscape/cardiology/journal/2001/v05.n04/mc0808.levi.html
3. Rotondi A, Kvetan V, Carlet J, Sibbald W. Consensus conference in critical care medicine. Crit Care Clin 1997;13:417-39.
4. Sachet DL. Rules of evidence and clinical recommendation on the use of antithrombotic agent. Chest 1989;952 Suppl:S2-4.
5. Balk RA. Pathogenesis and management of multiple organ dysfunction or failure in severe sepsis and septic shock. Crit Care Clin 2000;16:337–52.
6. Thys LG. Pathophysiology of coagulation and fibrinolysis in sepsis. Crit Care And Shock 1998;1:15–25.
7. Levi M. Sepsis and coagulation system. Adv Sepsis 2000;1:16–22.
8. Cate H. Pathophysiology of disseminated intravascular coagulation in sepsis. Crit Care Med 2000;28 suppl:S9–11.
9. Vervloet MG, Thys LG, Hack CE. De arangements of coagulation and fibrinolysis in critically ill patients with sepsis and septic shock. Sem Thromb Hemost 1998;24:33–44.
10. Hack CE. Tissue factor pathway of coagulation in sepsis. Crit Care Med 2000;28 suppl:S25–30.
11. Abraham E. Tissue factor inhibition and clinical trial results of tissue factor pathway inhibitor in sepsis. Crit Care Med 2000;28 suppl:S31–3.
12. Mammen EF. Antithrombin: Its physiological importance and role in DIC. Sem Thromb Hemost 1998;24:19–25.
13. Esmon E. The Protein C pathway. Crit Care Med 2000;28 suppl:S44–5.
14. Opal SM. Phylogenetic and functional relationship between coagulation and innate immune response. Crit Care Med 2000;28 suppl:S77–80.
15. Bick RL. Disseminated intravascular coagulation. A Clinical/laboratory coagulation in 48 patients. Am J Clin Path 1982;77:244-514.
16. Pralong G, Calandra T, Glauser MP, Schellekens J, Verhoef J, Bachman F. Plasminogen activator inhibitor-1: A New prognostic marker in septic shock. Thromb and hemost 1989;61:495-562.
17. Levi M, de Jonge E, Van der Poll T, Ten Cate H. Disseminated intravascular coagulation. Tromb Hemost 1999;82:695-705.

18. Yu M, Nardela A, Pechet L, Screening tests of disseminated intravascular coagulation: Guidelines for rapid and specific laboratory diagnosis. Crit Care Med 2000;28:1777-80.
19. Bick RL. Disseminated intravascular coagulation: Objective clinical and laboratory diagnosis, treatment, and assessment of therapeutic response. Sem Thromb Hemost 1996;22:69-88.
20. Bovill EG. Disseminated intravascular coagulation: Pathophysiology and laboratory diagnosis. Fibrinolysis 1993;7 Suppl 2:17-9.
21. Takahashi H, Tatewaki W, Wada K, Niwano H, Shibata A. Fibrinolysis and fibrinogenolysis in disseminated intravascular coagulation. Thromb Hemost 1990;63:340-4.
22. Bick RL. Disseminated intravascular coagulation: pathophysiological mechanisms and manifestations. Sem Thromb Hemost 1998;24:3-18.
23. Mammen EF. The Haematological manifestation of sepsis. J Antimicrob Chem 1998;41 Suppl A:17-24.
24. Bick RL. State of the art review. Disseminated intravascular coagulation: Objective criteria for clinical dan laboratory diagnosis and assesment of therapeutic response. Clin appl Thromb Hemostasis 1995;1(1):3-23.
25. Feinstein DI, Marder VJ, Colman RW. Consumptive thrombohemorrhagic disorders. In: Colman RW editor. Hemostasis and thrombosis. Basic principles and clinical practice. 4th ed. Philadelphia: J.B Lippincott; 2001. p.1023-63.
26. First Asia Pacific Consenssus Conference in Critical Care Medicine. Resucitation of patient in septic shock. Crit Care and Shock 1998;1(1):57-74.
27. Riewald M, Riess H. Treatment options for clinically recognized disseminated intravascular coagulation. Sem Thromb Hemost 1998;24(1):53-59.
28. Schuster HP. Epilogue: Disseminated intravascular coagulation and antithrombin III in intensive care medicine: Patophysiological insight and therapeutic hopes [editorial]. Sem Hemost Thromb 1998;24(1):81-2.
29. Du Toit HJ, Cotzee AR, Chalton DO. Heparin treatment in thrombin induce disseminated intravascular coagulation in the baboon. Crit Care Med 1991;19(9):1195-2015.
30. Corrigan JJ, Jordan CM. Heparin therapy in septicemia with disseminated intravascular coagulation. New Eng J Med 1970;283(15):778-82.
31. Corrigan JJ. Heparin therapy in bacterial septicemia. J Pediatr 1977;91(5):695-700.
32. Feinstein DI. Diagnosis and management of disseminated intravascular coagulation: the role of heparin therapy [abstract]. Blood 1982;60(2):284-7.
33. Levi M, Cate HT. Disseminated intravascular coagulation. New Eng J Med 1999;341(8):586-92.
34. Eisele B, Lamy M. Clinical experience with antithrombin III concentrate in critically ill patients with sepsis and multi organ failure. Sem Thromb Hemost 1998;24(1):71-80.
35. Lamy M, Eisele B, Keinecke HO, Delvos U, Thijs LG. Antithrombin III in patient with severe sepsis. A Randomized placebo-controlled double-blind multicenter trial. Proceeding of the 9th Congress of Intensive Care Medicine; 1996 Sept 24-28; Glasgow, UK. Monduzzi editore; 1996.
36. Fourrier F, Chopin C, Huart JJ, Runge I, Caron C, Goudemand J. Double-blind, placebo-controlled trial of antithrombin III concentrates in septic shock with disseminated intravascular coagulation. Chest 1993;104(3):882-8.
37. Fourrier F Jourdain M, Tournoys A. Clinical trial results with antithrombin III in sepsis. Crit Care Med 2000;28 Suppl 9:S38-43.