AETIOLOGICAL FACTORS, DIAGNOSIS AND TREATMENT OF DISSEMINATED INTRAVASCULAR COAGULATION – A STUDY IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Introduction: Disseminated intravascular coagulation is a syndrome, characterized by a systemic activation of the blood coagulation system. It results in the generation and deposition of fibrin, leading to microvascular thrombi in various organs contributes to the development of multi organ failure. It is always secondary to or associated with an underlying disorder.[1,2] The objectives of this study were to: describe the clinicopathological pattern of DIC, to find out the associated factors for DIC, and enlist different diagnostic tests and follow the therapeutic outcome and prognosis. It is a case series study. The study was carried out at Shaikh Zayed Hospital Lahore which is 750 bedded facility affiliated with FPGMI.

Subjects and Methods: Sociodemographic data like name, age, sex, address was collected. The history of the present illness was noticed with regard to severity of symptoms like fever, bleeding, cough, dyspnoea and altered consciousness. Patients were investigated for complete blood counts like Hb%, Platelet count, D-dimer, FDPs levels and fibrinogen level. Association factors for DIC were also noticed.

Results: In this study the most frequent association factor was found to be sepsis. Bleeding manifestations present in 90% of the patients, cough in 63.3% of the subjects. Patients with hypotension and altered consciousness were found to have a bad prognosis. Those treated with heparin infusion were not found to have a significant improvement in their clinical outcome.

Conclusion: DIC is an important acquired coagulation abnormality most frequently associated with sepsis requiring vigorous treatment with blood products and anticoagulants.

Key Words: Disseminated intravascular coagulation (DIC), D. dimers, Heparin.

INTRODUCTON

Disseminated intravascular coagulation (DIC) is a clinicopathological syndrome in which widespread intravascular coagulation is induced by procoagulants that are introduced or produced in the blood circulation and overcome the natural anticoagulant mechanisms.[1] The subcommittee on disseminated intravascular coagulation of the International society of thrombosis and haemostasis has suggested the following definition for DIC. An acquired syndrome characterised by the intravascular activation of coagulation with loss of localisation arising from different causes. It can originate from and cause damage to the microvasculature which if sufficiently severe can produce organ failure.[2,3] DIC indicates the transition from the localised, adaptive and compensated coagulation processes into maladaptive responses.[3] There are many different aetiological factors of DIC. The most important among them are infections, obstetric complications, malignant disorders, liver disease and different autoimmune disorders.[2] The presence of DIC increases the risk of mortality beyond that associated with the primary disease. The removal of its underlying cause does not necessarily alleviate the process in all cases.[2]

The first clinical observation on DIC was reported in the 19th century.[3,4] In 1834 it was reported that injection of brain material into animals caused wide spread clots in the blood vessels, thus providing the first description of DIC.[1] The mechanisms by which DIC can lead to bleeding were clarified in 1961.[1] Several simultaneously occurring mechanisms play a role in the pathogenesis of DIC. The most important among them are thrombin generation and impaired function of inhibitors of coagulation.[3]

Approximately 18000 cases of DIC occurred in US in the last year.[4] Mortality rates in major series of patients with DIC are 31% to 86%.[1] Overt DIC was found in 25 – 50% patients with sepsis and is a strong predictor of mortality.[5,6] Thus the new emphasis is on recognizing a non-overt stage rather than an overt and late stage of DIC.[6] Infectious diseases and malignant disorders together account for two third of DIC cases[1]. In paediatric patients with DIC

underlying aetiological agents was sepsis in 95.2% and major trauma in 4.8%.[7,8] In Pakistan mortality rate with DIC in obstetric patients is approximately 85%.[9,10] DIC occurs in pre-eclampsia 7%, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets, pre-eclampsia) 30% and in acute fatty liver of pregnancy 90% of the time.[9]

There has been a great reduction in DIC and mortality resulting from DIC due to better understanding of its aetiology, pathogenesis, clinical presentation, with better care of patient and vigorous treatment of DIC and the underlying cause.[7] There are many new different treatment strategies for this life threatening syndrome. New information about the pathophysiology and treatment of DIC promises new hope of an improved prognosis for this disorder which has been associated with unacceptably high mortality.[6] Unfortunately very few studies have been carried out in this aspect in Pakistan.[9,10] The objectives of this study were to describe the clinicopathological pattern of DIC, to find out the association factors for DIC and to enlist different diagnostic tests and follow the therapeutic outcome and prognosis.

METHODOLOGY

This is a case series study carried out at Shaikh Zayed Hospital Lahore, which is a 750 bedded hospital attached to Federal post graduate medical institute. Duration of this study was approximately six months i.e. from 29th February to 01st September 2009. It included thirty cases. Sampling technique was purposive non probability sampling. Inclusion criteria include all ages and both genders and cases of DIC on clinical basis. Exclusion criteria includes cases of DIC secondary to severe liver disease and with end stage renal disease. From all selected cases after informed consent, sociodemographic data like name, age, sex, address were collected. The history of present illness with regard to severity of symptoms like fever, bleeding, cough, dysponea and level of consciousness. Patients were examined for petechie, purpura, acral cyanosis, localised infections or signs of gangrene, signs of acute respiratory distress, level of consciousness and haemodynamic status. Patients were investigated for complete blood counts like Hb%, TLC, Platelet count, PT and APTT. D-dimers, FDPs levels and fibrinogen level were noted. Complete blood counts were performed on Sysmax KX 21. PT, APTT and serum fibrinogen levels were done on KC_4 Amulung coagulometer. Fibrinogen estimation was thrombin time based. D-dimers levels were performed with latex agglutination method and semiquantitative analysis was done. FDPs levels were done with latex agglutination method.

Patients were followed during their stay in the hospital. Association factors like infections, malignancy, obstetrical causes, and other miscellaneous causes for DIC were found out. Patients were treated with antibiotics, inotropic drugs, blood components therapy like fresh frozen plasma, whole blood, platelets and anticoagulants. Patients were followed up till they remained in the hospital. Treatment outcome of different patients was carried out. Patients either completely recovered or expired due to uncompensated DIC and end organ damage. All this data was entered in a proforma.

All collected informations were entered into SPSS version17 and analysed through its statistical package. Data was analysed in relation to sociodemographic data which included age and gender, findings in history which included history of bleeding, fever, altered sensorium, cough, dyspnoea physical examination findings like petechiae, signs of acute respiratory distress syndrome, hypotension, altered level of consciousness etc, causes and treatment out come. The variables were; pattern of disease in relation to sociodemographic profile and presented as frequency distribution tables, calculating mean and standard deviation for the numerical value.

The factors like infection, obstetric complications and development into malignancy were assessed for association with DIC. Different signs and symptoms were analysed for any significant association with outcome. Then being qualitative in nature, chi square test of significance was applied. p value $\leq$ 0.05 is significant.

Outcome of therapy like complete recovery or death of patients in terms of duration of disease, drug and outcome of diagnostic results were presented as proportions and ratios.

RESULTS

The study was carried out over a period of 6 months. Thirty patients were included from different departments e.g medical, surgery, gynaecology and obstetrics, gastroenterology, nephrology, intensive care units and accidents and emergency department. Patients were diagnosed as having DIC according to

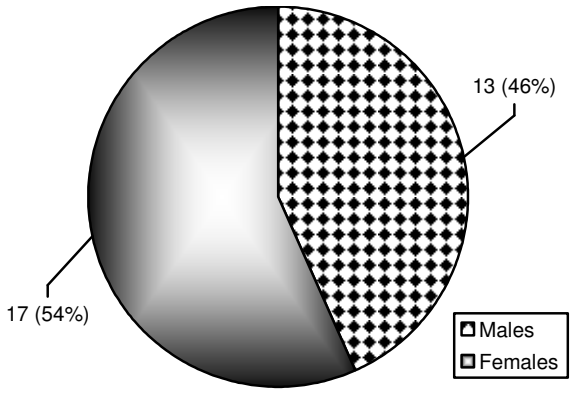


Fig. 1: *Male and female distribution in the study.*

criteria given by International Society of Haematology and Thrombosis.[1]

There were 13 (46%) males and 17 (54%) females in the study (Fig. 1). Mean age of patients was 35.2 ± 16.2 years). Most of the patients were in third decade. Mean age in male patients was 45 years and in female patients was 27 years.

The analysis of clinical features at presentation (Table 1) it was found that fever was present in 27 (90%) patients. It was associated with dyspnoea in 27 (90%) and cough in 19 (63%). Full blown ARDS developed in 23 (76.7%) patients during their stay. Twenty (66.7%) patients had documented sepsis which was secondary to urinary tract infections, chest infection, post operative infection and catheter related infections etc. Petechiae and bleeding from more than one site were present in 90% each.

Analysis of lab data (Table 2) revealed that Hb was subnormal in 23 (76%) patients. Mean Hb was 8.9 ± 3.6 g/dl. Total leucocyte count was elevated in 12 (40%) and subnormal in 5 (16.7%) patients. Platelet count was low in 17 (56%) at admission. Rest of the patients however revealed a downward trend in serial platelet count during course of the disease. Mean platelet count was 97 ± 98 × 10^9/l.

PT was prolonged (≥ 3 sec above normal) in 20 (66.7%) patients. APTT was prolonged (≥ 7 sec abo-

Table 1: *Signs and Symptoms in 30 Patients with DIC.*

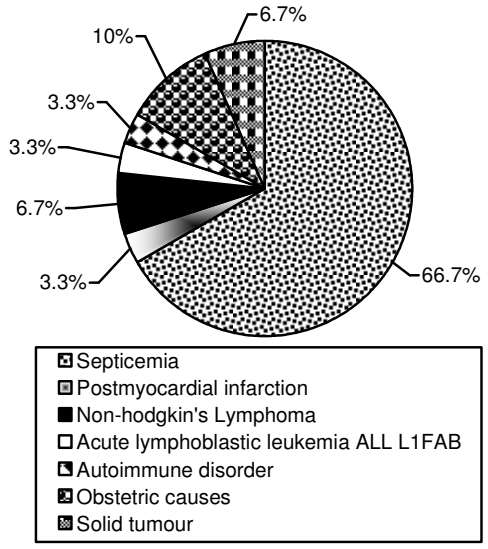
Sr. No.	*Symptom and Signs*	*Frequency (%)*
1.	Fever	27 (90%)
2.	Bleeding manifestations ≥ 2 sites	27 (90%)
3.	Petechiae	27 (90%)
4.	Dyspnoea	27 (90%)
5.	Altered consciousness	25 (83.3%)
6.	ARDS	23 (76.7%)
7.	Hypotension	22 (73.3%)
8.	Signs of Infection	20 (66.7%)
9.	Cough	19 (63.3%)

KEY: ARDS = Acute respiratory distress syndrome

Table 2: *Initial diagnostic tests in 30 patients with DIC.*

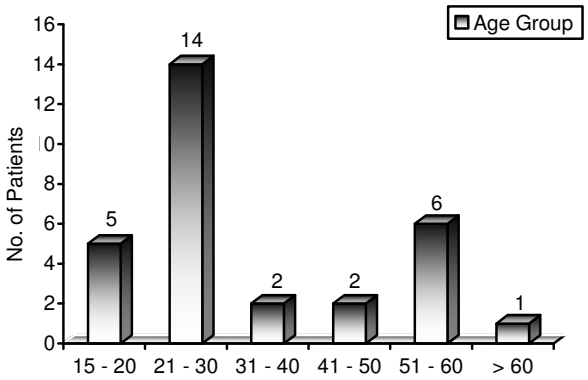
Sr. No.	*Diagnostic Tests*	*Mean ± SD*
1.	Hemoglobin (g/dl)	8.9 ± 3.6
2.	TLC (×10^9/ul)	11.3 ± 8
3.	Platelets (×10^9/ul)	97 ± 98
4.	PT (seconds)	23 ± 15
5.	APTT (seconds)	44 ± 22
6.	Fibrinogen (mg/dl)	309 ± 207
7.	D-dimers (ng/ml)	> 2000
8.	LDH (U/l)	695 ± 549

KEY: TLC = total leucocyte count
PT = prothrombin time
APTT = activated partial thromboplastin time
LDH = Lactate dehydrogenase



Septicaemia = 66.7%, Obstetric causes = 10%, Malignant disorders, 1. Solid tumor = 6.7%, 2. Non-hodgkin's Lymphoma = 6.7%, 3. Acute lymphoblastic leukemia ALL-L_1 FAB = 3.3%, Myocardial infarction = 3.3%, Autoimmune disorder = 3.3

Fig. 2: *Association factors of DIC.*



Mean age ± SD = 35.2 ±16.2 years
Key: SD = Standard Deviation

Graph 1: *Age Groups in the study.*

ve normal) in 18 (60%) patients. Mean fibrinogen level was 309 ± 207 mg/dl and low fibrinogen was found in only 9 (30%) the patients. FDPs were elevated and were > 20 ug/ml in 28 (93.3%) patients, moderately elevated level i.e between 5 – 20 ug/ml was seen in 2 (6.67%) patients. Mean LDH levels are 695 ± 549 U/l. It was markedly elevated i.e, more than 500 U/l in 10 (33.3%) patients.

D-dimers were significantly elevated (> 2000 ng/ml) in 100% patients and schistocytes on peripheral smear were seen in all patients.

Aetiological factors associated with DIC were noted in all patients (Fig. 2). In 20 (66.7%) patients, DIC was found to be associated with septicaemia which was secondary to chest infection, urinary tract infection, post operative wound infection, meningitis, catheter related infections and acute necrotising pancreatitis. DIC secondary to malignancy in 16.7% which included Non-Hodgkin's lymphoma in 6.7%, solid tumour in 6.7% and ALL in 3.3% the patients. DIC was secondary to obstetric complications in 10% which included missed abortion (6%) and intrauterine death (4%). A few cases of DIC were secondary to acute myocardial infarction and autoimmune disorders.

Patients were treated with specific treatment of the underlying cause, i.e. antibiotics to treat underlying infection, inotropic support for patients with cardiac decompensation, steroids for immune haemolysis, and chemotherapy for leukaemia / lymphoma.

Patients were treated with whole blood, blood components (FFP, platelets) and low dose heparin infusion for DIC. 16 of 30 patients recovered after treatment and 14 expired. FFPs were transfused to 29 patients, platelet trans-fusions to 4 and whole blood to 8 patients.

Different demographic features like age, gender and clinical features like fever, dyspnoea, altered consciousness, hypotension and ARDS were analysed for any significant association with an outcome (Table 3). Altered level of consciousness and hypotension were significantly associated with increased mortality (p value<0.05).

Table 3: *Association of demographic and clinical features with outcome in 30 patients with DIC.*

Features		*Recovered n = 16*	*Expired n = 14*	*p-value*
Age	≤40 years	13	8	0.15
	>40 years	3	6	
Gender	Male	6	8	0.29
	Female	10	6	
Fever	Present	15	12	0.47
	Absent	1	2	
Bleeding	Present	14	13	0.63
	Absent	2	1	
Dyspnoea	Present	14	13	0.63
	Absent	2	1	
Altered Conscious Level	Present	11	14	0.02*
	Absent	5	0	
Hypotension	Present	8	14	0.002*
	Absent	8	0	
Acute Respiratory Distress Syndrome	Present	13	10	0.53
	Absent	3	4	

*= Statically significant p value

Table 4: *Association of different treatment modalities with outcome in 30 patients.*

Treatment Modality		*Recovered n = 16*	*Expired n = 14*	*Total n = 30*	*p-value*
FFP	Used	15	14	29	0.35
	Not Used	1	0	1	
Platelet	Used	1	3	4	0.31
	Not Used	15	11	26	
Whole Blood	Used	5	3	8	0.68
	Not used	11	11	22	
Heparin	Used	10	7	17	0.49
	Not Used	6	7	13	
Inotropic Support	Used	1	11	12	0.01*
	Not used	15	3	18	

*= statistically significant p value KEY; FFP= fresh frozen plasma

Table 5: *Comparison of the association factors in present study with 4 different studies.*

Association factors %	*Spero JA et al, 1980*	*Kobayashi N et al, 1983*	*Matsuda M et al, 1983*	*Larcan A et al, 1987*	*Present study, 2009*
Septicemia	26%	16%	15%	15%	66.7%
Malignant conditions	24%	55%	61%	6%	16.7%
Obstetric disorders	_	5%	4%	38%	10%
Trauma and surgery	19%	_	2%	14%	_
Liver disease	8%	4%	6%	3%	*
Miscellaneous	23%	20%	12%	24%	6.7%

*patients with liver disease are excluded from this study

Although a number of patients (55.3%) recovered with FFPs infusion the results were not statistically significant (p-value > 0.05). Platelets and whole blood transfusions were also not associated with a significant difference in outcome

Infusion heparin was given to 17 patients, the effect on the outcome was not significant with p value > 0.05. The inotropic support was given to 12 patients in which 1 patient recovered and 11 expired. It was significantly associated with increased mortality (p value < 0.05). It actually reflects that patients who require inotropic support were in the stage of organ dysfunction (cardiac failure) and were associated with increased mortality. Other clinical and demographic features showed no significant association with outcome.

DISCUSSION

Many different diseases are complicated by disseminated intravascular coagulation. DIC is characterised by different signs and symptoms and laboratory findings of low platelet count, elevated D-dimers and deranged PT and APTT.[1,2]

One of the objectives of this study was to find out the association factors of DIC. In this study in 20 of 30 patients (66.7%) DIC was found to be associated with septicaemia which was secondary to chest infection, urinary tract infection, post operative wound infection, meningitis, catheter related infections and acute necrotising pancreatitis. DIC secondary to obstetric complications were present in 3 (10%) which included missed abortion 2 (6%) and intrauterine death 1 (4%). A few cases of DIC were secondary to acute myocardial infarction and autoimmune disorders.

Zeerleder et al reported clinically overt DIC in 30 – 50% of patients with sep-sis both with gram – positive and gram – negative organisms.[5] In the present study 3.3% patients had ALL and 6.7% had disseminated solid malignancy. A Japanese study by Tanaka et al it was found that in a hospital population 45% of the DIC cases were associated with malignancy.[3] However it was not specified whether this data was from a tertiary care unit or a cancer hospital. In another study it was seen that in patients presenting with acute leukaemia in particular ALL, DIC can be diagnosed in 15 – 20%.[11]

Infectious diseases and malignant disorders together account for approximately two thirds of DIC cases in major series, except for one study by Larcan et al 38% of the cases were obstetric patients.[1,12] According to Mushtaq DIC occurs in pre-eclampsia 7%, HELLP syndrome (haemolysis, elevated liver enzymes, low platelets, pre-eclampsia) 30% of time and in acute fatty liver of pregnancy 90% of the time.[9]

Different symptoms and signs of DIC were analysed and fever was present in 90% of patients. Bleeding manifestations ≥ 2 sites was present in 90% of patients, dyspnoea in 27 (90%) and cough in 19 (63%). Full blown ARDS developed in 23 (76.7%) patients during their stay. According to some other studies bleeding manifestations are seen in 76% and 87% of patients with DIC.[3] Bleeding manifestations may occur as a single clinical phenomenon or may be part of a complex derangement of the coagulation cascade due to DIC in gram negative sepsis.[13] Spero J A has reported bleeding manifestations in 77% of patients with DIC while Larcan et al has reported bleeding manifestations in 73%, respiratory dysfunction in 37%, neurological manifestations in 13% of patients in a case series.[1]

A subnormal Hb and platelets is seen in most patients in present study but in some patients the platelet count was normal initially and showed a fall from a higher count towards a lower value during course of disease .It has also been reported by Akca et al.[3]

Fragmented RBC's are present on the peripheral smear of all the patients included in the present study. According to Franchini et al these are seen in 50% of the cases with DIC.[14]

D-dimers are > 2000 ng/ml in all patients incl-

uded in the present study. According to diagnostic criteria of overt DIC given by ISTH D-dimers should be > 2000 ng/ml.[15] Patients with D-dimers < 2000 ng/ml were not included in the study. FDPs were elevated and were > 20 ug/ml in 28 (93.3%) the patients, moderately elevated level i.e. between 5 – 20 ug/ml was seen in 2 (6.67%) patients. According to Tayyab et al D dimers are more sensitive as compared to FDPs in the diagnosis of DIC.[10]

PT was prolonged (≥ 3 sec above normal) in 20 (66.7%) patients. APTT was prolonged (≥ 7 sec above normal) in 18 (60%) patients. According to Bick PT and APTT are unreliable tests and 50 – 75% of patients had a normal PT and 50-60% had a normal APTT in a series of patients.[16]

Plasma fibrinogen is a poor indicator of DIC in patients as it acts as an acute phase reactant[2] so in majority of patients in this study it was either increased, normal and in only 9 patients in this study it was less than 200 mg/dl. There is also increased synthesis of fibrinogen by the liver in DIC if there is no liver dysfunction.[2] In a study conducted in a series of patients with DIC the sensitivity of a low fibrinogen level for the diagnosis of DIC was only 28% and hypofibrinogenaemia was detected in very severe cases of DIC only.[3]

Altered level of consciousness and hypotension are significantly associated with outcome in the present study with a p value of < 0.05. This is due to the fact that patients presenting with these signs and symptoms have involvement of CNS and myocardium and evidence of end organ damage with associated high mortality.

Antibiotics were given to all patients in this study. Patients with malignancy received chemotherapy, patients with autoimmune hemolytic anaemia received steroids and obstetric patients were treated for underlying obstetric problem. In this study, supportive measures such as blood products like FFP, whole blood and platelet transfusion were also given to the patients. Sixteen of 30 patients survived, mortality among this cohart of overt DIC patients was 46%. FFPs were transfused to 29 patients, platelet transfusions to 4 and whole blood to 8 patients. Although a number of patients recovered with FFPs infusion the results were not statistically significant. (p value > 0.05). Platelets and whole blood transfusions were also not associated with a significant outcome.

According to many studies the treatment with plasma is not based on evidence from controlled trials. The only randomized controlled trial in neonates with DIC comparing the administration of FFP to blood exchange and any specific therapy failed to show any change in outcome.[17] This may be explained by the fact that many factors like underlying diseases, its effective treatment and stage of DIC in patients also affect the outcome.

Inj. heparin was given to 17 patients in this study out of which 10 were recovered 7 expired. Its use was not significantly associated with outcome (p value > 0.05). Heparin is mostly used in patients with clinical signs of extensive fibrin deposition like purpura fulminans, acral ischaemia or venous thrombosis.[18] Administration of heparin in a dose of 5 – 10 U/kg as a continuous infusion reportedly decreeses the rate of DIC after septic abortion.[3] A retrospective analysis of cases of DIC reported in literature found similar survival for patients treated and not treated with heparin.[2] Effects of LMWH delteparin as anti-DIC treatment has been studied in a multicentric double blind randomized trial. The underlying cause of DIC in most of these patients was malignancy and 13% of the patients suffered from infectious disease. In this study delteparin showed superior efficacy as compared to UFH in improving bleeding symptoms and in improving a subjective organic symptom score.[14]

Inotropic support was given to 12 patients out of whome 11 expired. The most probable explanation in most of these patients were in the phase of organ dysfunction with cardiac failure in the intensive care unit so the increased mortality is actually due to the stage of disease.[3]

It is ***concluded*** that disseminated intravascular coagulation is associated with many different clinical conditions. The data from this study indicate that DIC is most frequently associated with sepsis. Outcome was affected by complex interplay of many factors i.e. use of different blood products and anticoagulation with heparin infusion and the vigorous treatment of the underlying cause and stage of DIC.

REFERENCES

1. Seligshon U, Hoots KW. Disseminated intravascular coagulation. In: Beutler E, Lichman M, Coller B, Kipps JT, Kaushanky K, Prchal TJ, editors. Williams Hematology.7th ed. New York: McGraw Hill Professional; 2006: 1959-79.
2. Nash MJ, Cohen H, Lisener R, Machin SJ. Acquired coagulation disorders and vascular bleeding. In: Hoffbrand AV, Catovasky D, Tuddenham EG, editors. Postgraduate haematology. 5th ed. Oxford: Blackwell Publishing; 2005: 859-75.
3. Levi M, VanGorp EC, Cate HT. Disseminated intravascular coagulation. In: Hadin RI, Lux SE, Stossel TP, editors. Blood principles and practice of haematology. 2nd ed. Philadelphia: Lippencott Williams and Wilkins; 2002: 1275-301.
4. Rodger GM. Acquired coagulation disorders. In: Greer JP, Rodger GM, Foerster J, Paraskevas F, Leukens JN, Gleden B, editors. Wintrobe's clinical hematology. 11th ed. Philedelphia: Lippencot Williams and Wilkins; 2004: 1669-712.
5. Zeerleder S, Hack EC, Wuillemin AW. Disseminated intravascular coagulation in sepsis. Chest 2005; 128:

2864-75.
6. Toh CH, Dennis M. Disseminated intravascular coagulation old disease new hope. Br Med J 2003; 327: 974-7.
7. Toh CH, Downey C. Back to the future testing in disseminated intravascular coagulation. Blood Coagul Fibrinolysis 2005; 16: 535-42.
8. Oren M, Cingoz M, Diman M, Yilmaz S, Irken S. Disseminated intravascular coagulation in pediatric patients clinical and laboratory features and prognostic factors influencing the survival. Pediatr Hematol Oncol 2005; 22: 679-88.
9. Mushtaq MA. Disseminated intravascular coagulation in a patient with HELLP syndrome. Pak J Med Sci 2005; 21: 90-4.
10. Tayyab M, Mengal H, Tasneem T, Ditta A, Farooq M, Chaudhry N .Fibrinogen degradation products and d-dimer study in patients with preeclampsia. Pak Postgrad Med J 2003; 14: 10-3.
11. Aydin M, Flenaugh EL, Nichols M. Hemoptysis, anemia and respiratory failure: a rare initial presentation of acute leukemia. J Natl Med Assoc 2005; 97: 1550-2.
12. Bachmeyer C, Barrier A, Frazier A, Fulgencio JP, Lecomte I, Grateau G, et al. Diffuse large and small bowel necrosis in catastrophic antiphospholipid syndrome. Eur J Gastroenterol Hepatol 2006; 18: 1011-4.
13. Asakura H, Wada H, Okamoto K, Iba T, Uchiyama T, Eguchi Y, et al. Evaluation of haemostatic molecular markers for diagnosis of disseminated intravascular coagulation in patients with infections. Thromb Haemost 2006; 95: 282-7.
14. Franchini M. Pathophysiology, diagnosis and treatment of disseminated intravascular coagulation: an update. Clin Lab 2005; 51: 633-9.
15. Cauchie P, Cauchie Ch, Boudjeltia KZ, Carlier E, Deschepper N, Govaerts D, et al. Diagnosis and prognosis of overt disseminated intravascular coagulation in a general hospital – meaning of the ISTH score system, fibrin monomers, and lipoprotein-C-reactive protein complex formation. Am J Hematol 2006; 81: 414-9.
16. Bick RL. Disseminated intravascular coagulation: objective, clinical and laboratory diagnosis, treatment and assessment of therapeutic response. Semin Thromb Hemost 1996; 22: 69-88.
17. Schellongowski P, Bauer E, Holzinger U, Staudinger T, Frass M, Laczika K, et al. Treatment of adult patients with sepsis-induced coagulopathy and purpura fulminans using a plasma – derived protein C concentrate (Ceprotin). Vox Sang 2006; 90: 294-301.
18. Prandoni P. Venous thromboembolism risk and management in women with cancer and thrombophilia. Gend Med 2005; 2: 28-34.