

The association of disseminated intravascular coagulation with specific diseases

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Summary

Disseminated intravascular coagulation (DIC) is a syndrome that occurs in the course of a diversity of severe diseases and which is associated with an increased rate of morbidity and mortality. Although still an enigmatic syndrome, a recent consensus definition and criteria for clinical diagnosis have been proposed. The diseases responsible for 2/3 of cases of DIC are associated with infections (sepsis and disseminated viral infections) and malignancies (solid tumors as well as haematological malignancies). The presentation of DIC may be variable, ranging from acute thrombo-hemorrhagic symptoms in meningococcal sepsis, to chronic low grade DIC in certain malignancies. Other important groups of disorders are trauma (grade of DIC depending on the extent and origin of trauma), emergencies of pregnancy (abruptio placentae, amniotic fluid embolism, pre-eclampsia), snake bites, and major vascular disorders (aneurysm). The present availability of diagnostic tools to assess the presence and course of DIC should allow for the timely confirmation of this syndrome and may help to decide on the use of anticoagulant or other treatment, preferably after determining the efficacy in clinical trials. © 2002 Éditions scientifiques et médicales Elsevier SAS

disseminated intravascular coagulation / definition / classification

Résumé – Association entre la coagulation intravasculaire disséminée et diverses affections graves.

La coagulation intravasculaire (CIVD) est un syndrome qui survient dans l'évolution de diverses affections graves et s'associe à une augmentation de leur mortalité et de leur morbidité. Bien qu'il s'agisse d'un syndrome « énigmatique », un consensus a récemment été proposé pour définir le syndrome et les critères de diagnostic clinique. Deux tiers des CIVD sont observés au cours des infections (sepsis et maladies virales disséminées) et des cancers (tumeurs solides et maladies hématologiques malignes). La présentation de la CIVD est variable. Elle peut s'extérioriser par un syndrome thrombo-hémorragique aigu ou, au contraire, rester latente comme au cours de certains cancers. Les autres affections reponsables de CIVD sont les traumatismes (l'intensité de la CIVD dépend de l'extension et de l'origine du trauma), les pathologies obstétricales (hématome rétroplacentaire, embolie amniotique, prééclampsie), les morsures de serpent et les atteintes vasculaires majeures (anévrismes aortiques). Les tests biologiques détectant la présence et évaluant l'évolutivité de la CIVD devraient permettre de confirmer précocement le diagnostic et de décider des options thérapeutiques. L'efficacité des anticoagulants ou d'autres traitements doit faire l'objet d'études cliniques. © 2002 Éditions scientifiques et médicales Elsevier SAS

CIVD / définition / classification

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INTRODUCTION

Disseminated intravascular coagulation (DIC) has been an enigmatic syndrome for centuries. In the past, the clinical presentation of a patient with an unusual bleeding tendency, multiorgan failure or extensive thrombotic complications in the presence of significant laboratory abnormalities would raise the suspicion of DIC. Recently, a consensus definition of DIC has been proposed by the subcommittee of the International Society of Thrombosis and Haemostasis, which is primarily based on current insights into the pathophysiology of DIC:

“DIC is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction” [1].

This definition accentuates the fact that microvascular damage is the predominant site of injury related to DIC, but it leaves open diagnostic issues involved in clinical cases suspected from DIC. The latter is addressed by the same subcommittee in their proposed scoring system of DIC, which takes into account laboratory changes and clinical symptoms.

In considering clinical DIC several issues are important [2, 3]. First, the underlying disorder is of critical importance and its successful treatment offers the best chances of resolving DIC. Second, the manifestations of DIC depend on the nature and magnitude of the triggering factors. Dramatic cases of acute DIC are characterized by severe bleeding complications due to excessive consumption of clotting factors and fibrin occlusion of the microvasculature, which may follow the exposure to relatively large amounts of tissue factor containing material within a short period of time. Such a strong trigger overwhelms the available defense mechanisms resulting in uncompensated DIC. One of the most impressive clinical examples of acute DIC is purpura fulminans secondary to meningococcal sepsis with hemorrhagic skin necrosis and gangrene of the extremities. A more chronic form of DIC may exist in the presence of relatively localized and/or small amounts of tissue factor containing material such as in metastatic carcinoma, giant hemangioma, or dead fetus syndrome. A spectrum of clinical entities has been associated with DIC (*table I*). The frequency of DIC in these diseases however, varies considerably ranging from rare or doubtful to virtually obligatory (i.e. Gram-negative sepsis).

Table I. Clinical conditions that may be complicated by DIC.

| | |
|------------------------------------|---|
| -Severe infections / sepsis | |
| -Bacterial: | Gram-negative (endotoxin) -i.e. Neisseria meningitidis, E. coli, Salmonella typhi, Gram-positive (mucopolysaccharides) -i.e. Streptococcus pneumoniae |
| -Viral: | Hemorrhagic fevers i.e. Dengue, Ebola, Marburg, Hantaan Epstein-Barr, Cytomegalovirus, Varicella, HIV, Hepatitis |
| -Parasites: | Severe falciparum malaria |
| -Malignancy | |
| Solid tumors | Prostate, breast, ovarian, lung, gut |
| Hematological Leukemia | APL (AML M3), ALL, others |
| -Obstetric | Lymphomas Eclampsia and HELLP syndrome Placental abruption Amniotic fluid embolism Acute fatty liver disease of pregnancy Retained foetus syndrome |
| -Tissue necrosis | Trauma, fat embolism Burns, heat shock Incompatible or massive transfusions |
| -Liver disease | |
| -Prosthetic devices | LeVeen and Denver shunt Aortic balloon assist devices |
| -Vascular disorders | Kasabach-Merritt syndrome other vascular malformations Aortic aneurysms |
| -Severe allergic / toxic reactions | |
| -Snake bites | |
| -Hemophagocytosis syndrome | |

INFECTIOUS DISEASES

Sepsis is the most common underlying syndrome associated with acute DIC and Gram-negative as well as Gram-positive bacteria may be involved at approximately equivalent rates. In patients with sepsis, DIC appears to influence the clinical course and to enhance the mortality rate. Life-threatening complications from infections are a major and growing clinical problem, aggravated by the emergence and spread of antibiotic resistance of bacterial pathogens as well as an the increasing number of immune-compromised patients. In addition, certain clinical conditions, such as pregnancy, post-splenectomy, trauma or malignancies make patients particularly vulnerable to infection-induced DIC. Furthermore infections can aggravate disease-related thrombosis and the risk of bleeding by induction of thrombocytopenia, hepatic dysfunction and shock.

Today it is widely accepted that the activation of coagulation in severe infections, sepsis and septic shock is principally triggered by induction of tissue factor. In accordance with this finding is the fact, that several bacterial pathogens, such as *Neisseria meningitidis*, *Rickettsia* spp., *Staphylococcus aureus* as well as *Streptococcus sanguis* are able to induce the expression of tissue factor in monocytes and endothelial cells [4]. Endothelial cell damage followed by tissue factor expression is also a common feature of viral infections with direct infection of endothelial cells, such as HSV, adeno-, parainfluenza-, echovirus, measles, CMV, HTLV-1 and HIV as well as dengue-, Marburg-, Ebola- and Hantaan viruses. The most severe cases of viral hemorrhagic fever are complicated by DIC, whereas DIC is rare in other viral infections but has been reported occasionally in rotavirus, varicella, rubella, rubeola and influenza infections [4].

Endotoxin and a number of pro-inflammatory cytokines including TNF- α , IL-1, IL-6 and IL-8 are able to mobilize cellular adhesion molecules, which tether circulating platelets and leukocytes to vascular endothelium at sites of inflammation, and allow monocytes and neutrophils to migrate from vessels to the adjacent tissues. The study of the pathophysiology of infection related DIC, in models of human and primate endotoxemia and *E. coli* sepsis respectively, has been a subject of thorough investigation [5, 6]. Its discussion is however beyond the scope of this paper.

MALIGNANCY

In 1865 Trousseau described an association between migrating thrombophlebitis and the presence of malignancies [7]. Today it is well established that this syndrome is a manifestation of chronic DIC. Hemostatic abnormalities are frequently found in cancer patients, being detectable in about 50% of patients with localized tumors and in more than 90% of patients with metastatic disease, however the incidence of overt DIC appears to be much lower [8].

Solid tumors

Solid tumors have been shown to influence coagulation pathways by a number of different mechanisms:

Many solid tumors but also hematological malignant cells express tissue factor on the cell surfaces [9, 10], which in conjunction with factor VII activates the extrinsic pathway of coagulation. Tissue factor strongly correlates with fibrin deposition in the tumor stroma [11], reflecting perivascular activation of coagulation around permeable tumor vessels [12]. Independent from its clotting cofactor function tissue factor appears

to be involved in tumor metastasis [13] and angiogenesis [14], factors that may directly influence the course of malignancy and affect the occurrence of thrombosis. Tissue factor is formed and expressed by circulating monocytes in response to tumor antigens or complexes of tumor antigens and host antibodies [15]. A good correlation was found between the amount of tissue factor generated by monocytes in vitro and markers of activation of coagulation in patients with malignancies.

A cysteine proteinase with factor X activating properties is found in certain malignant tumors (i.e. lung and breast carcinomas, kidney and colorectal adenocarcinoma, various leukemia [16, 17]) and fetal tissues (amnion-chorion) and contributes directly to activation of coagulation (for a review see [18]). Other thrombogenic factors are related to enhanced adhesion and aggregation of platelets [19], or the secretion of mucin-like substances that may induce coagulation activation [20].

Hematological malignancies

DIC may complicate virtually all hematological malignancies, and a particular form is encountered in acute promyelocytic leukemia (APL). A characteristic of APL is its frequent association with a life-threatening hemorrhagic diathesis, which is responsible for 10-20% of early deaths [21-24]. Several factors are involved in the severe bleeding diathesis, such as DIC, hyperfibrinolysis, non-specific proteolysis and thrombocytopenia [22]. The physiological fibrinolytic response is exacerbated by the release of plasminogen activators (such as u-PA and t-PA) and other proteases from the leukemic cells [25-27] as well as by an acquired functional α 2-antiplasmin [28] and TAFI deficiency [29] contributing to the pronounced hyperfibrinolysis with high levels of fibrinogen and fibrin degradation products [30]. Despite the prominent role of the fibrinolytic system in patients with APL there is mounting evidence that hyperfibrinolysis is superimposed on a more common presentation of DIC, characterized by coagulation activation and fibrin deposition. Indeed diffuse thrombosis is found in 15-25% of patients at autopsy and recent studies have demonstrated tissue factor and cancer procoagulant dependent activation of coagulation in these patients [31]. Current treatment with all-trans retinoic acid (ATRA) has dramatically reduced the incidence of severe DIC in these patients [30] probably by reducing tissue factor expression on leukemic cells and substantial down-regulation of the cancer procoagulant, the latter paralleling cell differentiation [31, 32].

A high incidence of DIC has also been described in adult patients with acute lymphoblastic leukemia (ALL)

and in patients with de novo Philadelphia chromosome-positive ALL. While at presentation DIC was only detected in 10% of these patients, it was found in 80% during induction therapy. At present the pathogenesis of DIC in these patients is not clear [33].

PHYSICAL INJURIES

Polytrauma induced by physical force, burns or heat shock is associated with tissue damage and may lead to DIC in severely injured patients. The latter is triggered by a combination of mechanisms including release of tissue material into the circulation (fat, phospholipids), hemolysis, endothelial cell activation and acidosis due to hypoperfusion and tissue ischemia.

Trauma

Several mechanisms may be responsible for the development of DIC or aggravation of its manifestations in polytraumatic patients:

Entry of tissue factor into the circulation may occur due to either extensive trauma or by injury of tissues that contain abundant tissue factor, such as the brain. The catastrophic effects of brain extracts injected intravenously into animals were first reported in 1834 by Dupuy [34]. The first clinical observations on DIC and bleeding after brain injury were reported not until 1968, but well established thereafter [35-38]. Normally the course of DIC in brain-injured patients is self-limiting, however high mortality rates in brain-injured patients, were seen in patients with laboratory evidence of DIC [39, 40]. In fatal cases postmortem investigation confirmed the presence of microthrombi in brain, lungs, liver, kidneys and pancreas [41].

Trauma-induced hemorrhage and hemorrhagic shock contribute to depletion of hemostatic factors, accelerated coagulation and impaired clearance of procoagulants due to compromised control mechanisms. Circulatory shock also contributes to tissue hypoperfusion and ischemia. In addition, tissue damage may be influenced by post-ischemic reperfusion of oxygen radicals, calcium ion overload or release of pro-inflammatory mediators.

Other factors that may contribute to DIC in trauma patients are the dilution of essential blood components by massive transfusions, impaired production of clotting factors and natural anticoagulants as a consequence of injury of the liver by direct trauma, shock or thrombosis. Furthermore, adult respiratory distress syndrome (ARDS, systemic production and release of pro-inflammatory cytokines [42] and superimposed infections and sepsis may negatively influence the course of DIC in trauma patients [43].

Fat embolism is a specific entity, clinically characterized by a combination of respiratory insufficiency, neurological dysfunction and bleeding is caused by entry of bone marrow fat into the circulation. Three types of response to fat embolism were defined [44]: 1.) the hyperacute type with death soon after trauma due to "paradoxical" embolization. 2.) the classic type characterized by respiratory distress due to obstruction of small pulmonary vessels, interstitial pulmonary edema and slight consumption of hemostatic factors. 3.) a third type characterized by ARDS as a consequence of diffuse, extensive fat embolization to pulmonary vessels, hemorrhagic necrosis, pulmonary edema, formation of hyaline membranes in alveoli and prominent laboratory evidence of DIC. The latter is probably initiated by a combination of damaged pulmonary endothelium, release of tissue factor from ischemic pulmonary tissue and other sites of fat embolization, as well as inhibited fibrinolysis.

Burns

Burn wounds may either directly, by the induced tissue damage and exposure of tissue factor, or indirectly by secondary complications (infections, shock) elicit DIC. Indeed, in patients with extensive burns and laboratory tests suggestive of DIC, a hemorrhagic diathesis and the presence of vascular microthrombi in biopsy specimens of undamaged skin have been observed [45]. In addition to systemic activation, a significant local consumption of hemostatic factors takes place at burned areas as indicated by studies using radiolabeled fibrinogen and platelets [46].

Heat stroke

Heat stroke is characterized by a rise in body temperature to over 42 °C preceded by a collapse of the thermoregulatory system and is caused by high environmental temperature in combination with dehydration, the presence of infections and strenuous physical activity. Heat stroke may be complicated by severe DIC with widespread fibrin deposition and hemorrhagic infarction of various organs triggered by endothelial damage and probably tissue factor release from heat-damaged tissues. Type and magnitude of hemostatic derangement depend on both severity and stage of development of the syndrome [47].

OBSTETRICAL COMPLICATIONS

Normal pregnancy and childbirth are known to be associated with marked changes in the coagulation and fibrinolytic system, which convert pregnancy and child-

birth into a hypercoagulable state vulnerable to a spectrum of disorders ranging from venous thromboembolism to DIC. The latter is always secondary to specific obstetric complications such as placental abruption, amniotic fluid embolism with release of tissue factor into the maternal circulation, pre-eclampsia, the HELLP syndrome (hemolysis, elevated liver enzymes and low platelets), or uterine or systemic infection resulting in endothelial damage.

Pre-eclampsia

(Pre-) eclampsia is the most common obstetrical condition associated with activation of blood coagulation resulting in fibrin deposits in various organs in severe cases. Complications of severe cases are abruptio placentae in about 10% [48], the HELLP syndrome in up to 50% [49] and DIC in 6-13% patients [48, 50, 51]. The central pathophysiological trigger of DIC in severe eclampsia and the HELLP syndrome is probably the endothelial damage induced by cytokines produced by activated placental leukocytes and macrophages, accompanied by microangiopathic hemolytic anemia (MHA) as well as platelet adhesion and activation facilitating fibrin formation and deposition.

Abruptio placentae

Placental abruption is due to the rupture of uterine spiral arteries leading to partial or total separation of the placenta from the uterine wall during pregnancy and to acute DIC in severe cases. Known risk factors associated with this serious syndrome are hypertension, smoking [52, 53], use of cocaine, hyperhomocysteinemia [54-56], as well as thrombotic risk factors [57, 58]. The degree of placental separation has been correlated with the extent of fibrin formation and thrombocytopenia implicating local factors in the initiation of acute DIC. The incidence of placental abruption is reported to be 0.2-2% [59-63] and hypofibrinogenemia to be present in only 38% of patients [59, 64]. Consequently, not all patients with placental abruption develop DIC and only severe forms are associated with (hypovolemic) shock and fetal death. DIC accompanying placental abruption is self-limiting and if there is no improvement within 48 hours upon onset of DIC the presence of other complications, such as sepsis should be suspected.

Amniotic fluid embolism

Amniotic fluid embolism (AFE) is characterized by the passage of amniotic fluid into the maternal circulation usually during or just following childbirth however,

AFE has also been reported after cesarean section, first and second trimester abortions, abdominal trauma during pregnancy, amniocentesis and up to 48 h postpartum [65]. Classically, AFE presents as sudden onset of dyspnea and hypotension, often followed within minutes by cardio-respiratory arrest due to (extensive) occlusion of the pulmonary circulation by fetal debris, fat, meconium and other elements of the amniotic fluid. Maternal mortality is high with reported death rates between 60-86% [66, 67], mostly occurring within one hour of onset of the acute event and even though AFE is rare, occurring in 1/8.000 to 1/80.000 deliveries, it accounts for up to 10% of all maternal death [67]. Patients surviving the initial phase of AFE are at high risk (up to 40%, [67]) of developing DIC within a few hours and hemorrhage may be particularly severe from incision or puncture sites, the atonic uterus, the gastrointestinal tract or other organs. The potential of the amniotic fluid - containing functionally active tissue factor [68, 69] and a factor X activating substance [70, 71] - to activate coagulation and the subsequent exhaustion of coagulation factors and platelets, are responsible for the bleeding tendency. The mechanical obstruction in the pulmonary circulation by amniotic fluid debris possibly enhances local fibrin- platelet-thrombi formation.

Acute fatty liver of pregnancy

Another, rare obstetric complication associated with DIC is acute fatty liver of pregnancy (AFLP) affecting women in the latter part of gestation. AFLP is characterized by hepatic failure with jaundice, encephalopathy or even coma, coagulopathy and frequently hypoglycemia. Primary sources of DIC are most likely the combination of severe hepatic dysfunction associated with the substantial depression of antithrombin levels in virtually all patients [72]. The chances of both maternal and fetal survival are enhanced by early diagnosis allowing intervention in the form of prompt delivery of the infant. Hitherto, the cause of AFLP is unknown, but lately some cases (as well as of the HELLP syndrome) have been associated with recessively inherited deficiencies in fatty acid β -oxidation, the most common form being long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency [73].

Retained or dead fetus syndrome

Several weeks after intrauterine fetal death, patients may display laboratory signs of DIC, occasionally associated with bleeding. Apparently, tissue factor from the retained dead fetus or placenta gradually enters the

maternal circulation and initiates DIC, sometimes accompanied by significant fibrinolysis [74]. Progressive deterioration in laboratory coagulation tests and decline of fibrinogen calls for immediate evacuation of the uterus.

LIVER DISEASE

As most of the coagulation proteins are synthesized in the liver, which has also an important role in clearance of coagulation activation products, there has been considerable debate about the interpretation of clotting abnormalities in liver disease, especially in liver cirrhosis. According to one hypothesis a low grade DIC would be present, which is based on the following observations [75]: shortened half-life of radio-labeled fibrinogen and prolongation of its survival by administration of heparin [76, 77], failure of extensive plasma replacement regimens to significantly increase levels of hemostatic factors, suggesting continuous consumption of these factors, elevated blood levels of D-dimer and fibrinopeptide A, indicating thrombin generation [78]. Finally, heparin had beneficial effects in the management of some patients with hepatic failure [79].

In contrast, there are also arguments against an association of liver disease with DIC: a low incidence of microthrombi (2,2%) in tissues of patients who died of advanced liver disease [80], leakage of fibrinogen into the extravascular space and several hemostatic abnormalities caused by other factors than DIC or being not compatible with DIC (prolonged thrombin time due to dysfibrinogenemia, reduced production of coagulation factors and natural anticoagulants, increased FDP levels, probably as a consequence of primary fibrinogenolysis, increased (rather than decreased) factor VIII clotting activity).

According to a third hypothesis advanced liver disease is extremely sensitive to triggers of DIC, such as endotoxin, due to impaired clearance and reduced synthesis of inhibitors [81].

In specific cases of liver disease, clinical and laboratory signs of DIC have been observed after peritoneovenous shunt procedures for ascites (i.e. LeVeen shunt, Denver shunt). In those cases DIC may be triggered by the contact of blood with peritoneal fluid containing tissue factor, factor X activators, collagen or endotoxin [82-84].

VASCULAR DISORDERS

Large aortic aneurysms or giant hemangiomas (Kasabach-Merritt syndrome) may cause local activation of coagulation. Studies employing radiolabeled fibrinogen and platelets provided evidence that there is

consumption of these factors within the vascular lesions due to intravascular clotting and excessive fibrinolysis [85, 86]. Conceivably, there is concomitant local activation of coagulation, as well as release of large amounts of plasminogen activators by the abnormal endothelium lining the tumor vessel walls [87]. Systemic depletion of coagulation factors and platelets as a result of local consumption is common, although activated coagulation and fibrinolytic factors can 'leak' to the systemic circulation leading to systemic DIC.

Signs of DIC have also been found in other vascular lesions, such as Klippel-Trenaunay syndrome [88, 89], hemangiomas of the liver and spleen, hemangioendotheliosarcomas and in a small proportion of patients with aneurysms of large vessels, such as the aorta [90, 91].

SNAKE BITES AND OTHER EXOGENOUS HEMOSTATIC FACTORS

The administration of snake venoms into small vertebrates causes acute DIC within seconds. In accidentally bitten humans however, excessive bleeding or manifest thromboembolic disease is rare. Extensive abnormalities in coagulation and fibrinolytic functions are however frequently observed after snakebites. Many of these venoms have been isolated and functionally characterized.

Such examples include thrombin-like activators of fibrinogen [92]: i.e. batroxobin from *Bothrops atrox* (commercially available as Reptilase™, widely used in coagulation laboratories to monitor fibrinogen-fibrin reactions in patients receiving heparin, since it is not influenced by this anticoagulant) and activators of prothrombin [93]. One example of the latter venoms is ecarin, a metalloproteinase from the saw-scaled or carpet viper *Echis carinatus* cleaving only one (Arg320-Ile321) of the two factor Xa cleavage sites in Prothrombin [94].

FREQUENCY OF DIC AND CONCLUDING REMARKS

The present consensus diagnosis of DIC offers a conceptual framework of the microvascular involvement of this syndrome in serious underlying disease. The clinical diagnosis of DIC is based on the presence of an underlying disease in combination with laboratory tests indicating activation of coagulation, soluble fibrin formation and consumption of platelets and hemostatic factors. On the basis of the combined clinical and laboratory data three stages in the development of DIC may be distinguished: 1.) Compensated activation of the hemostatic system, 2.) Decompensated activation of the hemostatic system and 3.) Acute DIC with

Table II. Estimated incidence of DIC in various diseases.

| Disease | Incidence (n/total cases) | % |
|---|---------------------------------|-------|
| Severe infections and Sepsis | | |
| -Meningococcal septic shock (children) | 35 / 60 | 58-67 |
| -Septic shock | 20 / 30 | 73 |
| -Systemic inflammatory response syndrome (SIRS) | 44 / 60 | 83 |
| | 29 / 35 | |
| Malignancy | | |
| -All | 2 / 108 | 1.8 |
| -Solid | 7 / 718 | 1 |
| -Advanced lung cancer (postmortem) | 8 / 34 | 24 |
| -Acute promyelocytic leukemia (APL) | 13 / 21 | 62 |
| -Acute lymphoblastic leukemia (ALL) | 110 / 232 | 47 |
| -At diagnosis | 11 / 91 | 12 |
| -During induction therapy | 59 / 75 | 79 |
| Obstetrical | | |
| -HELLP syndrome | 15 / 183 | 7-8 |
| -HELLP with abruptio placentae | 22 / 303 | 42-60 |
| | 8 / 19 | |
| | 10 / 17 | |
| Aortic aneurysm | 17 / 3687 | 0.5 |

generation and deposition of fibrin with widespread microvascular fibrin formation in various organs. However, transition from an activated hemostatic system to overt DIC may not be readily discernable also due to the variable presentation of the underlying disease. As a consequence, the reported incidences and prevalence of DIC in various diseases vary widely depending on type of patients or definitions used to characterize DIC and comparison of different studies is difficult.

Although numerous diseases can provoke DIC only a limited number of disorders constitute major causes as may be inferred from retrospective clinical studies [95-97]. Together, infections and malignancies account for about 2/3 of DIC cases in most of the few larger series. The prevalence of DIC in other diseases is hard to estimate due to limited data (table II).

Today most of the published literature on DIC concerns its pathophysiology, which is well understood in general terms. Other aspects of DIC however, in particular those related to clinical management remain obscure. New insights in the pathogenesis of DIC and general application of standardized diagnostic criteria should allow for better prospective clinical (diagnostic and management) studies in diseases associated with DIC.

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