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Internal Medicine: 1976 Topics

Editors: Antti Louhija and Ville Valtonen, Helsinki

Publishers: S. Karger, Basel

Reprint (Printed in Switzerland)

Internal Medicine: 1976 Topics

13th Int. Congr. Internal Med., Helsinki 1976, pp. 224–236 (Karger, Basel 1977)

Disseminated Intravascular Coagulation in Septicemia: When to Treat and How

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Introduction

Over the last 10–15 years, disseminated intravascular coagulation (DIC) has been increasingly 'in'. What is its present state: is it only an interesting experimental phenomenon, or does it also kill sick patients? The evidence is that it does, and in this paper we shall review its case in septicemia, with emphasis on practical guidelines for diagnosis and therapy. We define DIC as the pathological process that follows extensive generation of thrombin in systemic blood. It is always a complication of serious underlying disease; episodes of DIC in such patients are probably quite common, and they may result in severe organ dysfunction and/or bleeding. Several reviews and monographs attest to the interest it has created among clinicians and researchers (1, 6, 10, 23).

Today, it is in the area of management of DIC that the largest problem remains. To treat or not to treat, that is the question. Widely different practices exist: some advocate rapid and energetic heparin therapy as soon as the diagnosis is established, while others claim that the coagulation defects will spontaneously repair themselves with clinical improvement of the underlying disorder. An important reason for this controversy is the lack of controlled clinical trials. To our knowledge there is only one, reporting no benefit of heparin therapy on the coagulation disturbances in acute hepatic necrosis (16). As the chance of obtaining results from properly controlled trials in the near future appears slim, we have tried to formulate practical guidelines for therapy based on existing data.

Pathogenesis

Septicemia leads to DIC through a chain reaction. The infectious agent somehow triggers the reaction, but clotting is usually released through one or more *mediators*. The reaction is often sped up by *accelerators*, and the final

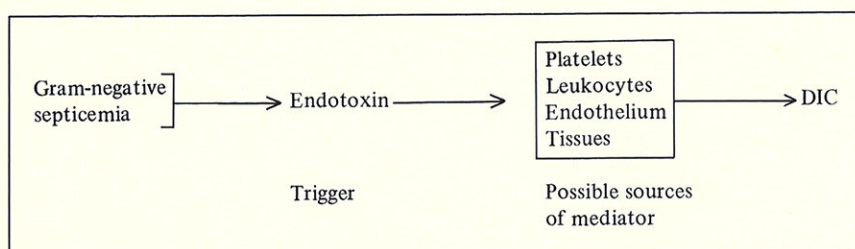


Fig. 1. During severe Gram-negative infections, it is postulated that bacterial endotoxin triggers DIC by releasing one or several mediators in an intermediate reaction.

result — the deposition of fibrin — is greatly influenced by *modifying factors*. Usually, these modifiers determine *if* and *where* fibrin is deposited.

The infection most often complicated by DIC is Gram-negative septicemia, and fulminant meningococemia in particular (7, 17, 23, 28). In this disorder, bacterial endotoxin is the primary trigger of DIC. A variety of other infections may also be accompanied by DIC, including Gram-positive septicemia, viral and rickettsial diseases, and malaria. In these disorders, we have no solid data about how clotting is triggered, but the speculation is that the infectious agents produce endothelial damage.

How Does Endotoxin Trigger DIC?

Endotoxins are lipopolysaccharide-peptide macromolecules in the outer layers of the bacterial cell wall. Endotoxins elicit, directly or indirectly, a large number of reactions affecting many organ systems in the host. Many research workers have injected different types of endotoxin into different animal species according to different dose schedules, and the result is a large collection of partly conflicting data.

The simplest solution to the triggering problem would be that endotoxin has a direct effect on the coagulation system. Although some recent studies indicate that endotoxin may activate Hageman factor directly (32), it is more likely that endotoxin works indirectly by releasing or generating a mediator of clotting, as shown in figure I. Admittedly, Hageman factor activation does occur in endotoxemia resulting in release of vasoactive substances both from the kinin and from the complement system, but these reactions appear to be secondary to vessel damage and bear mainly on the modifying factors (see below). These effects of endotoxin have recently been excellently reviewed by Cash (6).

Platelets and leukocytes are both likely sources for a mediator of coagulation (fig. 1). Both contain procoagulant activity (41), and both are clearly injured by endotoxin. For platelets endotoxin-binding membrane components have been described (22). The ability of platelet factor 3 to induce DIC is disputed (11,

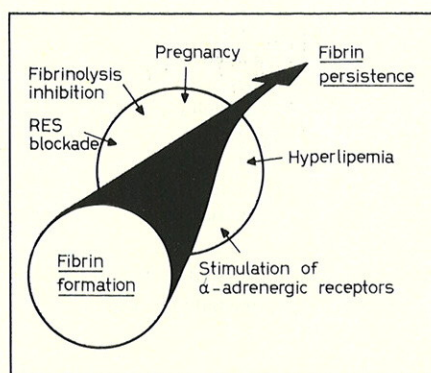


Fig. 2. Several factors modify the triggering stimulus. Generally, these factors determine if and where microthrombi will form and whether they will persist.

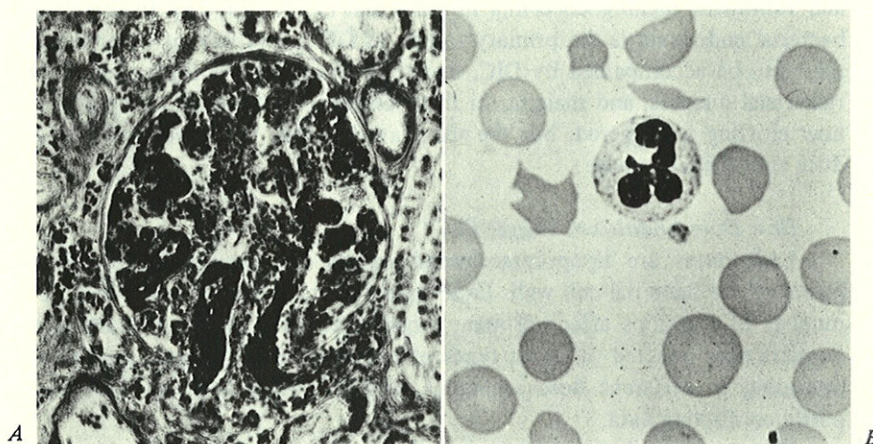


Fig. 3. *A* Consequences of fibrin microthrombi. *B* Erythrocytes are fragmented as they pass through vascular channels partly occluded by fibrin strands.

34), but *Margaretten and McKay* (29) demonstrated that thrombocytopenia prevented the occurrence of renal fibrin thrombi induced by endotoxin in the rabbit. Thus, no firm conclusion about the role of platelets in endotoxin-induced DIC can be drawn. Possibly, platelets may provide *accelerators* rather than *mediators* of coagulation (37). They also contain platelet factor 4 which precipitates fibrin monomer complexes (27).

A role for leukocytes in this reaction has been postulated since *Thomas and Good* (48) demonstrated that the presence of granulocytes was essential for the production of the generalized Shwartzman reaction in rabbits. Later research has

distinguished between two different possible functions of leukocytes in DIC. One is to serve as source of a mediator (26) which stems mainly from monocytes (42), and is greatly enhanced after exposure to endotoxin (35, 36). The other is by precipitating soluble fibrin monomers through the release of lysosomal cationic proteins (45). The fact that endotoxin-induced precipitation of soluble fibrin monomers did occur in granulocytopenic rabbits may invalidate this attractive hypothesis (33).

The endothelium as a source of mediator is the least investigated, but not the least likely possibility. The endothelium suffers severe damage after endotoxin injection (13, 15, 31). Neither the absence of leukocytes (14) or late complement components (12) nor the presence of heparin (15) prevent this endotoxin-induced injury. These data are based on experiments in animals, and we do not know to which extent they are valid in man. However, severe endothelial injury, be it primary or secondary, is probably an event also in septicemia in man. The injured endothelium may release mediators, and it must represent an ideal surface for the deposition and/or precipitation of soluble fibrin monomers.

Modifying Factors

The potency and quantity of the trigger does not alone decide the clinical outcome of the clotting disorder. Evidently, there are a number of systemic and localizing factors which determine whether the formed fibrin shall result in occluding microthrombi or be lysed, phagocytized or washed away. Some of the best known modifiers are shown in figure 2. The mechanisms responsible for precipitation of soluble fibrin monomers must also be included. Note that clot mediators and agents capable of precipitating fibrin monomers may stem from the same source.

Once formed, the deposited fibrin in small vessels (fig. 3 A) can soon impair organ function. The kidney is most vulnerable, but no organ is immune. The extent to which deposits of fibrin impair blood flow can be evaluated by examining the erythrocytes in the peripheral blood film (fig. 3 B)). Clinical and experimental data indicate that red cells are fragmented when they traverse narrow vascular channels partly occluded by fibrin strands (44).

Laboratory Diagnosis

The diagnosis of DIC rests on demonstrating the tracks of thrombin action: consumption of platelets and thrombin-sensitive coagulation factors (fibrinogen, factor V and factor VIII), low level of antithrombin III, the presence of soluble fibrin monomers in plasma, secondary fibrinolysis, and fragmented erythrocytes in the peripheral blood film. Many diagnostic tools are available, but diagnosis may be difficult and requires a high level of suspicion. This is mainly due to the

dynamic nature of the process. First, DIC often develops on top of a so-called hypercoagulable state characterized by high plasma levels of the consumable coagulation factors. Secondly, the synthesis of thrombin-sensitive clotting factors is stimulated by their own consumption. Thus, textbook profiles of consumed clotting factors are only found in pronounced and acute defibrination syndromes. For these reasons, the time-consuming and laborious specific factor assays have lost ground with the exception of fibrinogen assays. Our experience is that these and other specialized assays, including the highly specific and sensitive assay for fibrinopeptide A (39), are not necessary for the diagnosis. Besides, these tests are usually not available when they are most needed. We will therefore comment on six simple, rapid, 'middle of the night' guides to diagnosis.

Platelet count. Thrombocytopenia is a cornerstone in the diagnosis. Thrombocytopenia in septicemia can, however, result from at least two effects: first, direct damage to platelets by endotoxin or bacteria and, secondly, aggregation and subsequent removal induced by thrombin. Among 36 pediatric cases of septicemia, the most frequent single abnormality was thrombocytopenia (61% of all cases), but only a minority had DIC (9). In septicemia, severe thrombocytopenia warns of possible DIC and the need for replacement with platelet concentrates.

Peripheral blood film. The presence of fragmented red cells supports the diagnosis in a patient without evidence of other small vessel disease. However, it is by no means an obligatory finding. Screening of the blood film also indicates significant thrombocytopenia.

Fibrinogen determination. During acute septicemic states, we believe that fibrinogen assays can be relied upon as an important diagnostic parameter of DIC provided the result is interpreted with reference to the underlying disorder. It must be remembered that many inflammatory conditions have high fibrinogen levels due to increased synthesis. Thus, we would consider the finding of fibrinogen levels less than 150 mg/100 ml for low in septicemic patients, especially if they are pregnant. In severe DIC, however, frank hypofibrinogenemia will often be found. The bad diagnostic reputation that fibrinogen assays have had for some years is mostly due to the demonstration of normal or elevated levels in patients with chronic DIC, e.g. in malignant disease.

Thrombin time. The thrombin time is easy to perform and provides a lot of information. A prolonged thrombin time may result from a fibrinogen level below 50 mg/100 ml, the presence of heparin in the plasma, or the presence of FDP. If a fibrinogen assay is not available, it is helpful to know that a prolonged thrombin time due to FDP is usually not shortened by mixture of the patients' plasma with an equal part of normal plasma.

Ethanol gelation test. This test demonstrates the presence of soluble fibrin monomers in plasma (18). If care is taken in sampling (short stasis, wide-gauged needle), several studies show that the test is a reliable diagnostic tool in DIC.

False-negative results can be seen at fibrinogen levels less than 20 mg/100 ml and in the presence of high levels of FDP. Other sophisticated methods for the detection of soluble fibrin in plasma have been described (24), but will probably not come in wide clinical use. Addition of protamine sulfate to plasma results in precipitation (paracoagulation) in the presence of fibrin monomers or early fibrin degradation products (38). Because of this lack of specificity of the protamine sulfate test, we prefer the ethanol gelation test.

Fibrin degradation products. Practically all patients with DIC develop secondary fibrinolysis which is easily and rapidly detected by commercial kits. In our experience, the level of FDP must exceed 100 $\mu\text{g/ml}$ before a prolonged thrombin time can be demonstrated in a patient not receiving heparin (provided the fibrinogen level is within normal limits). Whether so-called primary fibrinolysis exists at all is still controversial.

An important part of the diagnostic routine is to freeze adequate amounts of citrated plasma for confirmatory tests requiring time-consuming or specialized techniques.

In conclusion, the diagnosis rests on the results of a spectrum of simple assays; no single test is diagnostic. Technically difficult and sophisticated assays are rarely called for, but the indicated assays should be repeated at intervals if doubts remain.

Therapy

Figure 4 summarizes the steps in the pathogenesis of DIC and outlines possible therapeutic approaches. Each step offers at least one possible mode of treatment, but only a few are in practical clinical use.

Treatment of the underlying clinical disorder. In caring for the patient with DIC, treatment of the clotting disorder is always a secondary concern. The primary goal is successful management of the infection. Vigorous treatment with antibiotics and rapid reversal of hypovolemia and acidosis will often make the clotting disorder disappear spontaneously. Some clinicians maintain that evidence of DIC is almost exclusively found in patients with hypotension (9, 30), and they suggest that DIC is the mediating mechanism producing shock in septicemia. We still do not know whether these conditions are independent or related manifestations of septicemia, but heparin treatment of children with septicemia improved the coagulation defects without improving survival (7). Therefore, heparin, does certainly not replace measures against endotoxin shock. Included in this anti-shock regimen is corticosteroid therapy. In pharmacological doses (e.g. hydrocortison 40 mg/kg), cortisone has many anti-shock effects, including stabilization of the lysosomal membrane. It also acts as an adrenergic blocking agent, relieving the vascular spasm caused by the abnormal action that adrenaline

Septicemia	Possible therapeutic approaches
↓	
Release of trigger	Injection of antitoxins
↓	
Release of mediator	Inhibition of platelet and/or leukocyte sequestration
↓	
Thrombin generation	Heparin therapy (table I); infusion of antithrombin III
↓	
Localization of fibrin thrombi	α -Adrenergic receptor blockade; inhibition of fibrin monomer precipitation
↓	
Persistence of fibrin thrombi; organ dysfunction and bleeding	Thrombolytic therapy; replacement of hemostatic factors

Fig. 4. Each step in the pathogenesis of DIC has theoretically at least one therapeutical approach.

and noradrenaline exert in the presence of endotoxin. The use of corticosteroids in the presence of endotoxin has been questioned, because the generalized Schwartzman reaction can be produced by a single injection of endotoxin in cortisone-pretreated rabbits (47). However, no harmful effects have been documented of acute, high doses of corticosteroids in endotoxin shock either clinically or experimentally. Therefore, corticosteroids should be used in septicemic shock. When there is evidence of DIC, it should be combined with heparin.

Release of trigger. Any approach which would inactivate the trigger or accelerate its excretion would of course be valuable. It has been suggested to neutralize endotoxin by specific antibodies (5), but clinical experience is so far lacking.

Release of mediator. To inhibit the release of a clot-mediator one must know its source. The source is still unknown, but a trial of the effect of dipyridamole would appear indicated, because this drug may have valuable effects both on the release of platelet mediators and on the precipitation of soluble fibrin monomers (20). Previously, *Harker and Slichter* (21) have demonstrated that dipyridamole corrects the increased platelet destruction in patients with arterial thromboembolism and vasculitis.

Thrombin generation. Anticoagulation with heparin is the treatment of choice. However, the indications for heparin treatment are far from clear-cut, and there are no well-controlled studies on the efficacy of heparin in septicemia with DIC. For this reason, it is difficult to evaluate the reported effect of heparin in patients with Gram-negative septicemia (17, 28, 30). Some of the best documented reports come from *Corrigan* and co-workers (7-9). In a clinical

study of 26 children with septic shock, heparin improved the consumption coagulopathy but not survival (7). Neither was the survival rate in septicemic rabbits improved by heparin, although fibrinogen consumption was abolished (8). These reports have made several clinicians doubt whether heparin has any place in the treatment of DIC (46). We believe, however, that heparin may be indicated after the following questions have been carefully considered:

Is the episode of DIC continuing? Heparin is of no value if the episode of clotting is over. If heparin then is given, nothing but its side-effects can be expected. Increasing levels of platelets and fibrinogen, decreasing FDP titers, and the ethanol gelation test turning negative, suggest that thrombin generation has stopped.

Is DIC the result of septicemia? Whether low-grade DIC and septicemia are related or independent manifestations is important, because in patients with cancer a low-grade DIC may be the result of the malignant disease itself (4). This category of patients will probably not benefit much from anticoagulant therapy. However, patients with septicemia and aggressive DIC should be given anticoagulant therapy.

Has DIC produced definite signs of impaired organ perfusion or bleeding? A confirmative answer to this question implies that the consumption coagulopathy is serious. Impending renal shut-down, increasing metabolic acidosis, ischemic necrosis and fragmented red cells in the peripheral blood film are important signs to look out for.

If the answer to all these 3 questions is yes, a sound rationale for heparin therapy can be outlined (table I). The first question identifies the clotting disorder, the second links it to an acute, curable disorder, and the third documents the severity of the process. Laboratory evidence alone does not represent an indication for treatment, as DIC is relatively common among hospital patients, often transient and of little clinical consequence.

The first hours of heparin treatment should always be considered a trial. We therefore recommend a cautious start, as indicated in table I (calculated for an adult person of normal weight) and careful monitoring of the clinical manifestations and the changes in the laboratory tests. It is not easy to monitor therapy, because commonly used clotting tests for this purpose are often abnormal before heparin is started. We recommend the following:

Clotting tests. Serial determinations of fibrinogen, FDP, platelets, thrombin time, and ethanol gelation test. Among these, fibrinogen, FDP, and the ethanol gelation test are the easiest to interpret. In septicemia, platelets may remain low for a number of days after thrombin generation has stopped, and failure to demonstrate increasing platelet counts during therapy does not imply that clotting still goes on.

Parameters of organ function. These include hourly urine output and serial determinations of serum creatinine and acid-base balance.

Table I. Therapy of DIC

	Findings	Therapy
Only laboratory evidence of ongoing DIC	Thrombocytopenia; consumption of thrombin-sensitive clotting factors; positive ethanol gelation test; increased level of FDP	Delay decision about heparin therapy; treat underlying clinical disorder and combat shock; repeat clotting tests at intervals and await effect of therapy
↓		
Associated with impaired microcirculatory perfusion as a consequence of DIC	Oliguria; increased serum creatinine; metabolic acidosis; fragmented erythrocytes	Heparin therapy: start cautiously by 500 IU/h by continuous intravenous infusion after an initial dose of 5,000 IU i.v.; increase to 1,000–1,250 IU/h if serious bleeding does not supervene
↓		
and/or hemorrhage	Skin bleedings; oozing from puncture wounds	Heparin therapy as above; replacement therapy with platelet concentrates and/or cryoprecipitate may be given <i>after</i> anticoagulant therapy has become effective

Heparin is continued until the septicemia has been brought under complete control. Bleeding may be both an indication for and a result of heparin therapy. If the former is the case (due to ischemic vessel damage, consumption of hemostatic factors or a combination of both), the hazards are obvious. If the indications for heparin therapy otherwise are met, treatment should be supplemented by the hemostatic factor(s) needed, but only *after* the anticoagulation has become effective. The minimum initial dose of replacement therapy is approximately 10 U of either cryoprecipitate preparations (which supply fibrinogen and factor VIII) or platelet concentrates. Acute cessation of the heparin effect can be accomplished by the intravenous injection of protamine sulfate [1.0–1.5 mg for 1 mg (100 U) of heparin]. However, this is rarely called for when heparin is administered by continuous infusion. Besides, some data suggest activation of coagulation by heparin-protamine complexes, both *in vivo* and *in vitro* (19).

As mentioned earlier, the level of antithrombin III is low in patients with severe DIC (49). It is a clinical experience that these patients need higher doses of heparin than others to obtain the desired anticoagulant effect. It has been

proposed to supply these patients with preparations of purified antithrombin III (2, 43).

Is there indication for prophylactic use of heparin in septicemia? One might argue that the main reason for the failure of heparin is that therapy is started too late. We do not recommend heparin prophylaxis with one exception: the obstetric patient with Gram-negative septicemia runs so high a risk of developing DIC with possible irreversible renal ischemic damage that the potential danger of heparin is more than counterbalanced by the apparent benefits (25).

Localization of fibrin thrombi. α -Adrenergic blocking agents (dibenzylamine or chlorpromazine, 5–10 mg i.v.) and fluid replacement combat shock and may, in addition, prevent localization of fibrin in the microcirculation, probably by improving flow.

Persistence of fibrin thrombi. Activators of fibrinolysis (streptokinase and urokinase) have a theoretical role in the treatment of microthrombi not lysed by secondary fibrinolysis. This approach appears dubious and potentially dangerous, because the procoagulant stimulus is not removed. Thus, thrombolytic therapy appears contraindicated before the episode of DIC has been stopped, and later indicated only in patients with a defective fibrinolytic system. Actually, the opposite situation, that excessive secondary fibrinolysis appears to provoke or contribute to bleeding, is more often the case. Here, heparin therapy may be followed by ϵ -aminocaproic acid administered by continuous intravenous infusion (1 g/h) until signs of improvement have been observed.

Conclusion

The septicemic patient faces many dangers, and DIC is only one of them. It is important, therefore, that the patient is managed on the basis of continuous clinical evaluation and judgement. If the patient dies in the acute phase, he usually dies *with DIC* but *from shock*, and it is important to see DIC in this overall perspective. One should also realize that diagnosis and therapy of DIC rest on simple rules, and the clinician should not allow himself to be overwhelmed by a 'DIC complex' due to complicated schemes and incomplete evidence.

The diagnosis of DIC should not be delayed until bleeding and organ failure make it obvious. It is necessary to look for the evidence in every patient, and six simple tests supply the evidence: platelet count, blood film, fibrinogen assay, thrombin time, ethanol gelation test, and FDP assay.

Treatment always starts with antibiotics and anti-shock measures. Large doses of corticosteroids should be given when shock is present or imminent. Anticoagulant therapy, i.e. heparin infusion, is indicated when there is evidence of ongoing and serious disseminated intravascular coagulation.

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