Thrombocytopenia and thrombosis in disseminated intravascular coagulation (DIC)

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Disseminated intravascular coagulation (DIC) is the physiologic result of pathologic overstimulation of the coagulation system. Despite multiple triggers, a myriad of laboratory abnormalities, and a clinical presentation ranging from gross hemostatic failure to life-threatening thrombosis, or even both simultaneously, a simplified clinical approach augmented by a few readily available tests allows prompt identification of the process and elucidation of treatment opportunities. Platelet counts in DIC may be low, especially in acute sepsis-associated DIC, yet increased in malignancy-associated chronic DIC. Thrombotic risk is not a function of the platelet count, and thrombocytopenia does not protect the patient from thrombosis. The stratification of both thrombotic risk and hemorrhagic risk will be addressed.

Case Presentations

Case 1: On his 50th birthday, this patient with known advanced hepatitis C was forcibly taken by his best friends to an oyster raw bar to eat raw oysters. Despite his pleas that he hated raw oysters, he swallowed a few. After a few hours of partying, he felt ill, developed chills, fevers, and confusions and was taken to the Emergency Room where staff considered him inebriated and placed him in a quiet, dark room. In fact his ethanol level returned at 180 mg/dL. An hour later he developed large ecchymoses all over his body. His PT was 16.7 seconds; his PTT 68 seconds; platelet count 48,000/μL; pH was 7.08, and analysis for D-dimer tests returned markedly positive. Blood cultures were drawn and broad spectrum antibiotic therapy started. The ecchymoses worsened, epistaxis began, lactic acidosis worsened, and the results of all the prior blood tests deteriorated. What is going on? What can be expected? What can we do for this patient?

Case 2: A 60-year-old man with a prolonged history of esophagitis and now esophageal obstruction was found to have adenocarcinoma of the distal esophagus and uneventfully underwent esophagectomy, relieving obstruction but having positive margins for tumor. A few days later, his right leg began to ache and became swollen; appropriate studies revealed a substantial deep vein thrombosis (DVT) in that leg. He was treated with heparin infusion and warfarin therapy was initiated. Six days later when his INR was 2.7 for the second consecutive day, heparin therapy was stopped and he was discharged. Within hours, the right leg slowly became significantly worse, and now his left arm, at the site of a recent IV line, quickly became painful and swollen. He was readmitted. His platelet count, which had been 300,000/μL preoperatively and had remained at that level at discharge, was 160,000/μL on readmission. What might be going on and what can we offer this man?

Disseminated intravascular coagulation (DIC) is a clinical diagnosis tempered by a few readily available laboratory tests. Supplemental studies can be ordered to solidify the diagnosis or in special research situations. Classic, acute DIC was best clinically described by Mant and King 30 years ago.[1] It typically induces hemorrhagic manifestations as predominated in Case 1. Chronic (and often occult) DIC was landmarked by the 1977 paper by Sack et al.[2] This type of DIC often is more thrombotic, as exemplified in Case 2. Either clinical situation remains extremely dangerous, both from the seriousness of the specific underlying disorder that initiates and promulgates DIC, but also from the hemorrhagic and/or thrombotic tendencies that are characteristic of all DIC. The historical approach to our understanding of DIC has been reviewed.[3]

Pathophysiology of DIC

DIC does not occur in isolation, as it is essentially always the result of some underlying problem, which typically is rather obvious (**Table 1**). When one reviews the clinical conditions that are associated with DIC, one sees a veritable litany of very ill patients in nearly every category of in-hospital medical care. Stepping back from this list, one can deduce that what is in common with these heterogeneous etiologies is cell injury and/or death such that coagulation is initiated in vivo in physiological response to the

Table 1. Processes that may induce disseminated intravascular coagulation (DIC).

Tissue damage	
	Trauma
	Crush injuries
	CNS injuries
	Heat stroke
	Burns
	Hemolytic transfusion reaction
	Acute transplant rejection
Neoplasia	
	Cancers
	Leukemias, especially acute promyelocytic leukemia
	Cancer chemotherapy
	Tumor lysis syndrome
Miscellaneous	
	Shock
	Cardiac arrest
	Near drowning, especially in fresh water
	Fat embolism
	Aortic aneurysm
	Giant hemangiomas
	Selected snake bites
Microorganisms	
	Gram-positive bacteria
	Gram-negative bacteria
	Spirochetes
	Rickettsiae
	Protozoa
	Fungi
	Viruses
Obstetric conditions	
	Abruptio placentae
	Placenta previa
	Retained dead fetus syndrome
	Amniotic fluid embolism
	Uterine abortion
	Toxemia of pregnancy

production of either thromboplastic agents directly (in cases in which tissue has been damaged to the point that its thromboplastic contents are released) or indirectly when monocytes and/or endothelial cells are physiologically stimulated to produce and secrete cytokines in response to injury thus initiating the extrinsic pathway of coagulation. Monocytes and endothelial cells that do not constitutively elaborate tissue factor (TF) do so when stimulated by pathogens that activate endothelial cells into elaboration and secretion of TF and von Willebrand factor (VWF). What separates this physiologic hemostasis from pathologic DIC is whether the prothrombotic substances released by the product of magnitude and duration of the stimulus outstrips the clearance of these prothrombotic substances by the reticuloendothelial system, physiologic inhibitors of coagulation, and the fibrinolytic system.

Should the coagulation system be stimulated to the point that thrombin circulates free from all physiologic inhibitors, circulating thrombin is then free to convert fibrinogen into fibrin systemically and to activate platelets, as well as activate factors V, VIII, and XIII, thus completing coagulation. Yet thrombin, via the thrombin:thrombomodulin (TM) complex, activates protein C, which then further activates the fibrinolytic system while inhibiting factors Va and VIIIa. The fibrinolytic system is also activated via endothelial release of tPA, which in turn activates plasmin. Plasmin, once free of its inhibitors, is then free to degrade systemically factors V, VIII, XIII, as well as any nascent fibrin clots and even fibrinogen itself, generating the characteristic fibrin degradation products (FDPs). An appreciation of these multiple pathways, often acting at cross purposes to one another, is what allows one to fathom the laboratory and clinical perturbations of DIC.

This pathologic perturbation of a physiologic process produces thrombosis ("an unwanted clot at an unwanted time in an unwanted place"), particularly in the microcirculation. This accounts for the inappropriate deposition of fibrin and platelets in the microcirculation, with subsequent organ ischemia resulting in the characteristic hypofibrinogenemia and thrombocytopenia seen in the circulating blood. Accordingly, the term "consumptive coagulopathy" is an accurate alternative name for DIC.

Clinical Manifestations of DIC

There is a spectrum of thrombosis and hemostasis in all cases of DIC; by definition, each or both may be encountered. One of the more common causes of acute DIC is sepsis. This form of DIC is characterized by a trend toward more bleeding than thrombosis, particularly as observed at the bedside. The characteristic thrombosis that one might see in septic-generated DIC is purpura fulminans (PF). An example of an occult thrombosis is adrenal vein thrombosis with its inevitable subsequent adrenal hemorrhage, producing the so-called Waterhouse-Friderichsen syndrome. One of the more common chronic causes of chronic DIC is tumor-initiated DIC. This hypercoagulability of cancer in its pluperfect form is called Trousseau syndrome (**Table 2**). Despite their abbreviated half-lives, circulating levels of fibrinogen and platelets are often normal, if not even slightly increased, in this slower type of DIC. Therefore, hemorrhage is not as characteristic of cancer-initiated DIC as is thrombosis with overt manifestations as DVT and pulmonary embolism (PE) as well as thrombosis in the central nervous system CNS and the abdominal organs.

DIC is frequent in trauma patients, particularly those having impaired cardiac output to include shock and its accomplices, acidosis and hypothermia. That these are synergistic

Table 2. Features of Trousseau syndrome.

Clinical
- Recurrent migratory thrombophlebitis
- Unusual sites of thrombosis: axillary/subclavian veins; superficial veins of the neck, thorax, or abdomen; visceral or cerebral veins
- Failure to respond clinically to warfarin
- Usually respond clinically to heparin but may relapse immediately after discontinuation
- May appear to be "heparin resistant" because of rapid consumption of heparin
- May simultaneously experience arterial thrombosis and hemorrhage
- Associated with nonbacterial thrombotic endocarditis
- Tumor often small or occult adenocarcinoma

Laboratory
- No laboratory test sensitive or specific
- A shortened PTT may be encountered in some cases
- Platelets and antithrombin III levels are usually decreased
- Red blood cells may show changes consistent with microangiopathic hemolysis

in promulgation of this coagulopathy has been repeatedly shown in the trauma literature.[4] There is a progression from dilutional coagulopathy during the resuscitation of trauma patients to the eventual development of frank DIC unless and until hypothermia and acidosis can be corrected by prompt resuscitation of the patient. Hemostasis works neither at low pH nor with hypothermia.

Laboratory Manifestations of DIC

Mant and King[1] demonstrated plasma from the vast majority of patients suffering from acute classic DIC had abnormalities in prothrombin times (PT) and partial thromboplastin times (PTT) as well as thrombocytopenia and decreased fibrinogen levels. Nearly all these patients also had significant elevations of FDPs. Ironically, a shortened PTT has been observed early on or even prior to DIC in some cases.[5,6] The International Society of Thrombosis and Haemostasis (ISTH) Subcommittee on DIC promulgated a scoring system revolving around these readily available tests[7] (**Table 3**) and validated this simplified approach,[8] thereby negating the need for more complex DIC batteries. Even this ISTH-DIC laboratory test protocol is not without some misgivings, particularly if deployed in incorrect clinical situations (such as ambulatory patients with neither bleeding nor thrombosis) and mimics of DIC (such as dilutional coagulopathy). Three patients in these three different pathophysiologic conditions may present with identical laboratory parameters, as outlined in **Table 3**. Although all three patients have similar laboratory abnor-

Table 3. Laboratory testing is limited in discriminating among these three clinical situations.

	Case A		Case B		Case C	
	Chronic, stable, severe hepatic insufficiency		Dilutional coagulopathy		Disseminated intravascular coagulation	
	Level	Score	Level	Score	Level	Score
ISTH DIC TESTS*						
Platelet count/μL	80,000	1	70,000	1	60,000	1
D-dimer, μg/mL	2	2	2	2	3	2
PT, seconds prolonged	6	2	7	2	6	2
Fibrinogen, mg/dL	85	1	70	1	90	1
Total ISH score		6		6		6
Other Coagulation Tests						
ATIII level, % normal (nL)	30-50		30-50		30-50	
Plasminogen level, % nL	30-50		30-50		30-50	
Most coagulation factors, % nL	30-50		30-50		30-50	
Factor VIII activity, % nL	80-200		30-50		50-80	
PTT 1:1 mix with plasma	Usually corrects		Always corrects		Rarely corrects	
Other Features						
Pathophysiology	Decreased protein synthesis		Effects of dilution		Increased consumption	
Thrombin generation	Intact but sluggish		Maintained		Excessive	
Systemic hemorrhage	Uncommon		None		Characteristic	
Systemic thrombosis	Rare		None		Characteristic	
Hematologic treatment	Nonspecific		Platelets, fresh frozen plasma, cryoprecipitate		Aimed at any instigating circumstance	

These levels represent ranges typically encountered within such patient scenarios.
*ISTH Scoring algorithm: platelet count (> 100,000 = 0; < 100,000 = 1; < 50,000 = 2); elevated fibrin-related marker (no increase = 0; moderate increase = 2; strong increase = 3); prolonged prothrombin time (< 3 sec = 0; > 3 but < 6 sec = 1; > 6 sec = 2); fibrinogen level (>1.0 g/L = 0; <1.0 g/L = 1). Maximal score, 8; if score ≥ 5, compatible with DIC; if score <5, not affirmative for DIC.
ISTH indicates International Society of Thrombosis and Haemostasis; DIC, disseminated intravascular coagulation; PT, prothrombin time, ATIII, antithrombin III; PTT, partial thromboplastin time.

malities, more information is garnered by observing the patient and understanding the pathophysiology, which allows the clinician to distinguish Case A (chronic, stable, ambulatory severe hepatic insufficiency) from Case B (dilutional coagulopathy), and from true DIC as represented in Case C. Clearly, bedside information is extremely important, not only in the correct diagnosis but in prognostication and, more importantly, what treatment opportunities, if any, are revealed by determining the correct underlying process.

Many have attempted to augment these simple, readily available tests in efforts to not only further define DIC but to generate subclassifications and prognostic formulations. That these efforts have actually added to our understanding, let alone altered our treatment or prognosis, has not been proved. In classic acute DIC one would expect and often will find perturbations in concentrations of plasma antithrombin III, plasminogen, and alpha-2-plasmin inhibitor. Recently it has been demonstrated that the von Willebrand factor cleaving protease (ADAMTS-13) is markedly decreased in sepsis-related DIC and portends renal failure.[9] These tests are more expensive, less readily available, and often return too late to significantly alter the approach in this dynamic and rapidly evolving illness.

Accordingly, one can now produce a short focused laboratory approach supporting the clinical diagnosis of DIC (**Table 4**). These tests serve to bolster one's high pretest probability in a patient with unexplained bleeding, thrombosis, or often both. This set of laboratory tests is recommended.

Recognizing the strong tendency toward having objective, reproducible and numerical quantification systems in clinical studies, the ISTH-DIC scoring system is frequently employed. This is a legitimate effort. Some have divided DIC into "non-overt" and "overt" DIC. The question is whether this attempt to standardize definitions is of sufficient utility to overcome the vast heterogeneity among all patients who manifest the final common pathway we call DIC. For instance, one might theorize three different patients, all of whom who may be septic from pneumococcus. They may each have DIC and may even have similar ISTH-DIC scores but clearly are all associated with different prognoses either with or without treatment; even the treatment of each patient differs. An example might be a young college student, who, following what was thought to be a viral pneumonia, actually developed pneumococcal pneumonia and now has a parapneumonic empyema that on occasion leaks, causing brisk DIC. A second case, also characterized as pneumococcal sepsis, would be a middle-aged man who underwent splenectomy for staging of Hodgkin disease three decades ago. He has been well, but now suddenly develops chills, fevers, and prostration from post-splenectomy fulminant pneumococcal sepsis. The third case could be a 70-year old man with chronic obstructive pulmonary disease and multiple myeloma who now has pneumococcal sepsis. The notion that a numerical score derived from such a heterogenous group of patients could serve all needs at all times is somewhat stretched. Admittedly, it would be very difficult to accrue enough similar patients with each precise type of DIC to generate a more understandable system currently.

Table 4. Clinical diagnostic criteria for disseminated intravascular coagulation (DIC) aided by selected laboratory tests.

- Patient bleeding, thrombosing, or both, typically with progressive organ dysfunction.
- An underlying illness or process that may cause tissue damage, cell death, or production/release of tissue factor (TF).
- Usually some perturbation exists of simple, readily available tests such as thrombin time (TT), prothrombin time (PT), partial thromboplastin time (PTT), fibrin degradation products (FDP), D-dimer, or platelet count. These values may markedly change as the clinical situation changes.

The cause of death in DIC patients according to most clinical reviews is more of a function of the underlying cause, particularly if that cause is resistant to therapeutic measures. Pathologic bleeding and pathologic thrombosis conspire against the patient. Multiorgan dysfunction syndrome (MODS) is a frequent consequence of DIC and is usually due to bleeding into organs or thrombotic alterations in various organs to include the hepatic, cardiac, central nervous, renal, and pulmonary systems.

Therapeutic Considerations

A basic tenet involving one's approach to DIC is that, if an underlying condition is responsible for triggering, promulgating, and continuing the pathologic free circulation of both plasmin and thrombin, one's treatment is directed at reversing that cause. All patients should be resuscitated aggressively to optimize maintenance of fluid status, blood pressure, temperature, and pH. Those patients whose DIC triggers are most readily approached (typified by the obstetrical catastrophes) do very well, whereas those with chronic irreversible underlying diseases that are more difficult to resolve (such as sepsis in a granulocytopenic cancer patient with liver disease) are more difficult to treat.

Since the very beginnings of our unraveling of DIC, there has been vigorous discussions of whether replenishing a patient's plasma coagulation factors and platelets do more damage than not. On the one hand, one wishes to keep enough procoagulant factors and platelets to afford

hemostasis, yet any "extra" has been accused of "fanning the fire." Most suggest that fibrinogen levels should be kept above 50 mg/dL yet less than 100 mg/dL, whereas platelet counts might be maintained in the area of 50,000/μL, as these are held to be minimally effective levels. The source for fibrinogen usually employed is cryoprecipitate (on the order of 10 "units" of cryoprecipitate with each unit containing about 200 mg of fibrinogen). Fresh frozen plasma (FFP) is rarely recommended but frequently used (**Table 5**).

At first thought, if antithrombin III is the primary inhibitor of circulating thrombin and circulating thrombin is a defining component of acute DIC, it would seem intuitive that antithrombin III replacement would have efficacy, but such has not proved to be the case in human trials. Infusion

Table 5. Role of blood products in treatment of disseminated intravascular coagulation (DIC).

RBCs	Keep hemoglobin in range of 6 to 10 g/dL
Platelets	Depends on risks for bleeding, not just the platelet count. Risk for bleeding high if less than 20,000-30,000/μL especially if due to decreased production; less so if due to sequestration or shortened platelet survival; nil if due to thrombotic causes (TTP or HIT). In DIC, reasonable target range is 50,000/μL
FFP	Enormously overrated in treatment of DIC, especially since recent evolution of our understanding and danger of TRALI. Some indication to supplement RBC transfusions in "total body exchange" situations
Cryoprecipitate	Probably best source of fibrinogen. Reasonable target is to keep fibrinogen levels between 50 and 100 mg/dL

TTP indicates thrombotic thrombocytopenic purpura; HIT, heparin-induced thrombocytopenia; and TRALI, transfusion-related acute lung injury.

Table 6. Potential therapeutics for disseminated intravascular coagulation (DIC). Table modified from Dempfle.[12]

Agent and rationale	Comment
The Heparins	
If thrombosis is a risk or a problem, then inhibiting thrombin's action seems plausible	No randomized controlled trials published. Venous thromboembolism prophylaxis is ICU standard and seems rational. Heparin may worsen bleeding if used with ATIII therapy. If using heparin for therapy, do not use PTT to monitor; use heparin levels.
Antithrombin III	
ATIII is consumed in nearly all reports of DIC. Bolstering its level might increase clearance of thrombin	Large KyberSept[13] trial showed no benefit yet increased bleeding when used with low-dose heparin. In septic DIC and in patients not receiving heparin, ATIII reduced mortality 15%.[14] A systematic review[15] of three studies gives odds ratio of 0.65 for DIC septic patients not receiving heparin. ATIII infusions decreased mortality by 25% in a group of 32 burn patients with DIC features.[16]
Human Activated Protein C (APC)	
Theoretically inhibits thrombin generation mostly at microvascular level. By decreasing WBC release of tumor necrosis factor-alpha (TNFα), APC may also be anti-inflammatory	Aoki et al[11] compared APC to heparin, finding increased bleeding in heparin group and decreased bleeding with APC group compared with bleeding at study entry but no effect on multiorgan dysfunction syndrome with either. Their battery of coagulation studies all improved, APC greater than heparin, but no difference in complete recovery from DIC. Death rate was 20% in APC group and 40% in heparin group.
Drotrecogin Alfa (DrotAA) (recombinant activated ProC)	
Rationale similar to human APC	Generally used in sepsis independent of DIC. DrotAA decreased mortality (risk ratio [RR] 0.71 in overt DIC and RR of 0.81 in non-overt DIC) in PROWESS study[10] with trend to more bleeding but less overt thrombosis.
Activated Recombinant Human Factor VII (rhFVIIa)	
Typically used as a final option to increase production of thrombin in hemorrhaging patient resistant to all other efforts	If circulating thrombin is thought to be a major culprit, rhFVIIa could be dangerous to administer in DIC. In order to work, thrombin must be able to be generated so might be expected to not work in massive heparin overdosage or in situations having no fibrinogen and/or platelets. Several small case series[17-19] suggest possible efficacy in patients with DIC.
Recombinant Human Soluble Thrombomodulin (ART-123)	
Thrombomodulin (TM) is an endothelial-bound sink for circulating thrombin.	Aoki's group[20] compared infusion of ART-123 against low-dose heparin infusion in DIC from cancer or infection. ART-123 compared to heparin gave better improvements in coagulation tests and clinical bleeding yet no significant decrease in mortality. Side effects fewer with ART-123 than with heparin infusion

of preparations of activated protein C (APC) has shown some success, particularly in decreasing mortality with severe sepsis (**Table 6**).

The use of heparin in DIC remains controversial. In many studies, to include Mant and King's early study,[1] death from hemorrhage appeared to be increased by the aggressive use of heparin. Antifibrinolytic agents, such as EACA, may be advocated and are usually employed only late in cases characterized by extreme ongoing hemorrhage. Because of the ever-present circulation of thrombin, thrombin inhibition by the prerequisite infusion of heparin is strongly advised before the infusion of EACA in order to minimize a thrombotic catastrophe.

On one hand that the ISTH-DIC score is really measuring something of value is supported by the data from the PROWESS study of use of APC versus placebo in sepsis-related DIC,[10] which showed a very clear and present rise in mortality as a function of ISTH-DIC score. On the other hand, studies such as Aoki et al,[11] when investigating the efficacy of human APC in patients with DIC of all types, showed that the infusion of APC resulted in statistically significant improvement in selected DIC battery scores compared with heparin; however, there was no significant difference (P = .3) in the rate of complete recovery of DIC within those two groups.

The PROWESS investigators also noted that the ISTH-DIC scoring system consciously or unconsciously is used more to evaluate for hemorrhagic risk than thrombotic risk in DIC.[10] At times there was a correlation with clinical hemorrhage, while at other times there was not. They noted that there are fewer laboratory means to quantify thrombotic risk, and at present thrombosis is determined almost exclusively by clinical findings that lack both sensitivity and specificity. Therefore, it is possible that any of the investigative metrics used to study a treatment for DIC has little chance of proving a causative change in hemorrhagic risk and even less chance that the studied treatment has an effect on thrombotic risk.

If DIC represents both hemorrhagic and thrombotic risks, what is the clinician to do? First, of course, is to identify the underlying cause and approach that as aggressively as possible. Second is to estimate the relative evidence favoring hemorrhage and favoring thrombosis using one's best clinical judgment (some suggestions are listed in **Table 7**). Third, consider supportive therapy with blood and blood products (some suggestions are listed in **Table 5**). **T**he status of some potentially available remedies in DIC management, none of which are to be viewed as standard of care as yet, are discussed in **Table 6**.

What About Our Two Patients?

For Case 1, the clinical diagnosis (later confirmed by blood and stool cultures) was that the patient had acquired *Vibrio vulnificus* septicemia from ingestion of raw seafood. Antibiotic therapy was initiated. He rapidly developed purpura fulminans and, because this skin necrosis was rapidly advancing, it was elected to administer heparin by infusion at a rate to give therapeutic plasma levels of 0.4 to 0.6 u/mL but without published evidence this therapy would prove effective. He worsened as MODS progressed and he expired from cardiovascular collapse. Autopsy showed microvascular changes consistent with DIC, advanced hepatic cirrhosis, and adrenal infarction/hemorrhage.

For Case 2, it was clear that despite (or because of?) heparin prophylaxis this patient was rapidly developing new DVTs and "relapsed" on warfarin therapy. Our working diagnosis was Trousseau syndrome. Because it was possible (low

Table 7. Bleeding versus thrombosis versus both?

	Favors thrombotic risk	Favors hemorrhagic risk
History	Prior thromboses Known hypercoagulability Known hemostatic defect	Prior hemostatic failure
Bedside Observations	Thrombotic manifestations may include stroke, acute myocardial infarction, acute renal failure, DVT, PE, or purpura fulminans	Epistaxis, bleeding from IV sites or wounds, petechiae and ecchymoses strongly supportive if present, yet strongly negative if all are absent
Tempo of DIC	Sub-acute or chronic DIC	Acute fulminant DIC
Putative initiator of DIC	Cancer	Sepsis/trauma
Acidosis, shock, hypothermia	Neutral	Strongly positive for hemorrhage
Labs: Platelets < 50,000/μL	No protective effect	Indicates hemorrhagic risk

DVT indicates deep venous thrombosis; PE, pulmonary embolism; and DIC, disseminated intravascular coagulation.

probability) that he had HIT, he was initially treated with fondaparinux 7.5 mg SQ until his screening ELISA test for HIT returned negative. Fondaparinux was continued for ease of outpatient management. His thromboses rapidly responded and he has remained on that fondaparinux dose for the past year without clear evidence of tumor recurrence.

Disclosures

Conflict-of-interest disclosure: The author receives honoraria from GlaxoSmithKline.
Off-label drug use: Use of fondaparinux in possible HIT.

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